7IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Stephen D. PACETTI	Examiner: NGUYEN, Phu Hoang
Serial No.: 10/725,698	Art Unit: 1791
Filed: December 1, 2003	Confirmation No. 3424
Title: Temperature Controlled Crimping	Customer No. 45159

Mail Stop: **Appeal Brief-Patents**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Dear Sir:

This appeal brief is submitted pursuant to the Notice of Appeal that was filed on February 3, 2010 in response to the Final Office Action dated September 3, 2009.

REAL PARTY IN INTEREST

The real party in interest with regard to this appeal is Abbott Cardiovascular Systems Inc., with its primary place of business at 3200 Lakeside Drive, Santa Clara, California, 95054. The assignment by the inventor, Stephen Pacetti, to Advanced Cardiovascular Systems, Inc., was recorded at Reel/Frame 014777/0211 on December 1, 2003. Abbott Cardiovascular Systems Inc. purchased the vascular device division and all relevant intellectual property including the instant application of Advanced Cardiovascular Systems, Inc. (Guidant Corporation) in April 2006.

RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences related to or that might have any bearing, direct or indirect, on the Board's decision in this appeal.

STATUS OF CLAIMS

(1) Claims 1-75 have been canceled.

(2) Claims 76-83 (reproduced in Appendix A, attached) are pending and have been rejected in the Final Office Action mailed September 3, 2009 (reproduced in Appendix B, attached), and form the subject of this appeal.

(3) There are no other claims or withdrawn claims.

STATUS OF AMENDMENTS

The amendment filed on May 18, 2009 was entered and resulted in the Final Office Action mailed September 3, 2009.

SUMMARY OF CLAIMED SUBJECT MATTER

Claim 76 is the only independent claim (all the claims are reproduced in Appendix A, attached). It recites:

> 76. A method of making a medical device, comprising:
> (a) providing a stent having a coating comprising a polymer and a drug, the polymer having (1) a glass transition temperature below room temperature and (2) a shore hardness of 60A to 80D or 80A to 60D;

(b) positioning the stent on a balloon of a catheter assembly; and
(c) mounting the stent on the balloon, wherein the temperature of the coating during the mounting is at a temperature below room temperature to increase the shore hardness of the polymer by 10 to 50 percent.

As described in the "Background," stent crimping is the act of affixing the stent to a delivery catheter or delivery balloon so that the stent remains affixed to the catheter or balloon until the physician desires to disengage the stent from the catheter or balloon (specification, page 1, lines 21-23). Various types of crimping devices are described on pages 2 and 3 of the specification, including roll, collet, sliding wedge and iris crimper. Crimping devices and methods were developed for all metal stents, but not those which include a polymeric component such as a drug delivery polymeric coating (*Id.* at page 3, lines 17-20). Since biopolymers used with stents are softer, weaker and less durable than stent metals, traditional crimping apparatus and methods damage the polymeric components (*Id.* page 3, lines 23-27).

Depending on the type of polymer used, a crimped coating can exhibit adhesive failure or cohesive failure (*Id.* at page 13, line 9 to page 14, line 2). The various embodiments of the present invention provide a method of reducing or eliminating such damages. For polymers that have (1) a glass transition temperature lower than room temperature AND (2) a shore hardness of 60A to 80D or 80A to 60D, stents can be mounted on a balloon at a temperature below room temperature to increase the shore harness of the polymer by 10 to 50 percent to prevent coating damage (*Id.*, page 17).

GROUNDS OF OBJECTION AND REJECTION TO BE REVIEWED ON APPEAL

(1) Whether claims 79 and 80 are improper dependent claims under 37 CFR § 1.75(c) for failing to further limit the subject matter of independent claim 76.

(2) Whether claims 76-83[1] are unpatentable over Hijlkema et al. (U.S. 2002/0143382) ("Hijlkema") in view of Pacetti (U.S. Patent No. 6,574,497) and further in view of Rosenthal et al. (U.S. 2003/0144727) ("Rosenthal"). The three references are produced in Appendix C, D and E, attached.

ARGUMENT

(1) Objection of claims 79 and 80 under 37 CFR 1.75(c) for failing to further limit independent claim 76:

Appellant respectfully requests reversal of this objection.

Claim 76 recites "wherein the temperature of the coating during the mounting is at a temperature below room temperature," which provides for the upper limit of the claimed temperature range. Claim 79 provides that the "temperature is between -60 deg. C and room temperature," which provides the lower limit of the claimed temperature range. Claim 76 further limits claim 76 by providing the lower end of the temperature scale.

The same holds true for claim 80. Claim 80 also provides the lower limit for the claimed temperature range. For example, if the glass transition temperature of the polymer is 10 deg. C. (a glass transition temperature falling below room temperature as claimed in paragraph (a) of

claim 76) then the claimed temperature range would be between 10 deg. C (lower end) and room temperature (upper end).

Appellant respectfully submits that both claims 79 and 80 do further limit the claimed temperature range in paragraph (c) of claim 76.

(2) Rejection under 35 U.S.C. § 103(a) over Hijlkema in view of Pacetti and further in view of Rosenthal:

Appellant respectfully requests reversal of this rejection.

Claim 76 recites that the polymer for the stent coating has (a) a glass transition temperature below room temperature AND (b) a shore hardness of 60A to 80D or 80A to 60D.

First, the Examiner has indicated that "Hijlkema discloses the coating comprising a polymer (paragraph 21) and a polymer can have a Tg below or above ambient temperature depending on the ambient temperature." Appellant respectfully disagrees with this statement. Hijlkema, in paragraph [0027], teaches coating polymers "could include SIBS polymers (styrene-isobutylene-styrene) and any other suitable polymers." "SIBS" does not have a single glass transition temperature but, rather, has a separate Tg for each block. The polystyrene block has a Tg of approximately 95 deg. C. Accordingly, the glass transition temperature could be well above room temperature, depending on the quantity of the polystyrene block.

With respect to Pacetti, the Examiner has relied on that reference solely for its teaching of poly(vinylidene fluoride-co-hexafluoropropylene) ("PVDF-HFP") (col. 9, line 5-25) which is recited in claim 82 of the instant application. One skilled in the art will appreciate that PVDF

[1] The Examiner rejected claims 76-82 on page 2 of the office action. Appellant considers this to be a harmless

homopolymers have a Tg of about -30 deg. C, which is below room temperature. However, more significantly, it has been noted in the art that HFP homopolymers have a Tg of 152 deg. C. This certainly suggests that for copolymer with a high content of HFP, the Tg could be well above room temperature.

As for the shore hardness of the polymer, similar dependencies to the chemical constituents of the polymer are equally applicable as well and dictate the end mechanical properties for the polymer.

Second, not withstanding the quantity of the moieties which alter the mechanical and temperature properties of the polymer, a variety of other variable also play a significant roll in the Tg and mechanical properties of polymers. As indicated on page 14, lines 19-27 of the specification:

> Tg of a given polymer can be dependent on the heating rate and can be influenced by the thermal history of the polymer. Furthermore, polymer chemical structure heavily influences Tg by affecting polymer mobility. Generally, flexible main-chain components lower Tg and bulky side groups raise Tg. Similarly, increasing flexible-side-group length lowers Tg and increasing main-chain polarity increases Tg. Additionally, the presence of crosslinks can increase the observed Tg for a given polymer, and the presence of a drug or therapeutic agent can alter the Tg of a polymer due to plasticization effects. The magnitude of these plasticization effects depends on the miscibility and compatibility of the drug and polymer and the loading of drug in the polymer. (emphasis added)

Third, on page 3 of the Final Office Action, the Examiner has noted that "it is submitted that poly(vinylidene fluoride-co-hexafluoropropylene) inherently has the claimed properties of

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typographical error which does not affect this appeal so as to merit any discussion.

glass transition temperature being below room temperature and shore hardness being 60A to 80D or 80A to 60D."

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " MPEP 2112, quoting In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (emphasis added).

As indicated above, just because Pacetti recites by name the claimed polymer PVDF-HFP, this does not mean that Pacetti's PVDF-HFP harbors the same recited properties of claim 76. As indicated above, high content of HFP could bring the glass transition temperature well above room temperature. Since PVDF-HFP could possibly have a glass transition temperature below room temperature, this mere probability, in and of itself, is clearly inadequate to support the basis for "inherency."

Claim 76 also recites that for polymers that have a glass transition temperature below room temperature and (2) a shore hardness of 60A to 80D or 80A to 60D, the temperature of the coating during the mounting is at a temperature below room. (emphasis added) Hijlkema fails to teach "temperature below room temperature," as recited by claim 76. The reference teaches the temperature being "close to its glass transition temperature" ([0020]) or "approximately 20 deg. Celsius above the glass transition temperature" ([0030]). Pacetti and Rosenthal do not cure this deficiency either.

Finally, claim 76 also recites that for polymer that have a glass transition temperature below room temperature and (2) a shore hardness of 60A to 80D or 80A to 60D, the temperature of the coating during the mounting is at a temperature below room temperature to increase the shore hardness of the polymer by 10 to 50 percent. Appellant concedes that Hijlkema teaches increasing the hardness of the coating; however it fails to provide any indication whatsoever to what extent the coating needs be hardened, more significantly increasing it 10 to 50% for coatings that have a glass transition temperature below room temperature AND (2) a shore hardness of 60A to 80D or 80A to 60D.

The Examiner, in support of his contention of obviousness to increase the shore hardness of the polymer by 10 to 50%, has relied on well established precedent that "[w]here the general conditions for a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation" citing, In re Aller, 220 F.2d 454, 456, 105 USPQ 223, 233 (CCPA 1955).

Appellant respectfully submits that the Examiner's reliance on In re Aller is flawed. In In re Aller, it is imperative that the reference teaches "the general conditions for a claim." As indicated in Aller, the claimed process which was performed at a temperature between 40 deg. C and 80 deg. C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100 deg. C and an acid concentration of 10%.

In stark contrast to the case at bar, Hijlkema fails to recognize or recite the general conditions of the claim -- namely, the polymer having (1) a glass transition temperature below room temperature AND (2) a shore hardness of 60A to 80D or 80A to 60D. The only facts that are disclosed in Hijlkema is to make polymers harder and only one polymer, SIBS, is listed. As

mentioned above, SIBS could have a glass transition temperature well above room temperature. Since the general conditions of the claim is utterly ignored by Hijlkema, one skilled in the art would not have optimized the hardness by 10 to 50%.

As indicated in the specification (*see example,* pages 12, 13, 17 and 18), crimping is done in a temperature region based on the properties of the polymer designed to minimize on one hand cohesive or deformation failure and on the other hand adhesive failure. If the polymer remains or becomes too hard during crimping, adhesive failure of the coating will occur. If the polymer remains or becomes too soft during crimping cohesive or deformation failure of the coating will occur. Nowhere in Hijlkema is this balance between adhesive and cohesive failure recognized which would motivate one skilled in the art to derive the claimed parameters of the present invention. In sum, increasing the shore hardness by 10 to 50% for polymers having (1) a glass transition temperature below room temperature AND (2) a shore hardness of 60A to 80D or 80A to 60D maintains the proper balance between adhesive and cohesive failure.

With respect to dependent claims 77, 78, 79, and 80, Hijlkema (or the other references in combination) fails to teach the temperature being below the glass transition temperature; the temperature being below -30 deg. C.; the temperature being between -60 deg. C. and room temperature; and the temperature being between room temperature and the glass transition temperature. The Examiner has rejected dependent claims 77, 78, 79, and 80 as being obvious over Hijlkema as supported by In re Aller, stating that it would be obvious to one ordinary skill in the art to perform routine experimentation to deduct the recited temperature ranges.

Again, Appellant respectfully disagrees. Aller is based on the reference teaching the general conditions of the claim. Nowhere in Hijlkema is the two principal conditions of independent claim 76 recognized -- namely, (1) a glass transition temperature below room

temperature AND (2) a shore hardness of 60A to 80D or 80A to 60D. The temperature ranges recited in independent claims 77-80 are fundamentally based on the satisfaction of these two conditions in order to produce superior coatings. Further, as indicated above, Hijlkema merely teaches making the coating harder. The reference utterly fails to recognize the balance between cohesive or deformation failure versus adhesive failure. Hijlkema fails to recognize that if the coating remains or becomes too soft during mounting cohesive for deformation failure of the coating will occur and if the polymer remains or becomes too hard during crimping, adhesive failure of the coating will occur. The adjustment in temperature maintains the proper balance between adhesive and cohesive failure.

CONCLUSION

The Examiner has failed, as a matter of law, to set forth a *prima facie* case for 35 U.S.C. § 103 obviousness of claims 76-83 over Hijlkema, Pacetti and Rosenthal. Appellant therefore respectfully requests that the Board reverse all of the presented rejections as well as the objection and order the application to pass to issue.

Date: 4/5/10

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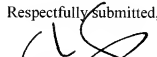
Respectfully submitted,



Cameron Kerrigan
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EVIDENCE APPENDIX

Attached hereto are the following Exhibits:

A. Claims Appendix

B. Final Office Action mailed September 3, 2009

C. U.S. Publ. Pat. App. No. 2002/0143382

D. U.S. Pat. No. 6,574,497 to Pacetti

E. U.S. Publ. Pat. App. No. 2003/0144727

Appendix A – Claims Appendix

76. A method of making a medical device, comprising:

(a) providing a stent having a coating comprising a polymer and a drug, the polymer having (1) a glass transition temperature below room temperature and (2) a shore hardness of 60A to 80D or 80A to 60D;

(b) positioning the stent on a balloon of a catheter assembly; and

(c) mounting the stent on the balloon, wherein the temperature of the coating during the mounting is at a temperature below room temperature to increase the shore hardness of the polymer by 10 to 50 percent.

77. The method of claim 76, wherein the temperature is below the glass transition temperature.

78. The method of claim 76, wherein the temperature is below -30 deg. C.

79. The method of claim 76, wherein the temperature is between -60 deg. C. and room temperature.

80. The method of claim 76, wherein the temperature is between room temperature and the glass transition temperature.

81. The method of claim 76, wherein the act of mounting comprising applying a crimping pressure on the stent to secure the stent to the balloon.

82. The method of claim 76, wherein the polymer is poly(vinylidene fluoride-co-hexafluoropropylene) or poly(butyl methacrylate).

83. The method of claim 76, wherein the drug is paclitaxel, docetaxel, rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, and 40-O-2-(2-hydroxy)ethoxyethyl-rapamycin.

Appendix B

UNITED STATES PATENT AND TRADEMARK OFFICE

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G3535US01

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/725,698	12/01/2003	Stephen D. Pacetti	50623.232	3424

7590 09/03/2009

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EXAMINER	
NGUYEN, PHU HOANG	
ART UNIT	PAPER NUMBER
1791	
MAIL DATE	DELIVERY MODE
09/03/2009	PAPER

FINAL OFFICE ACTION

RESPONSE DUE: 12/3/09

NTC of APPEAL DUE: 3/3/2010

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DOCKETED

SEP 09 2009

BY AV Atty RA

SQUIRE, SANDERS & DEMPSEY

Office Action Summary	Application No.	Applicant(s)	
	10/725,698	PACETTI, STEPHEN D.	
	Examiner	Art Unit	
	PHU H. NGUYEN	1791	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/28/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

Claims 79-80 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 79 and 80 recites "the temperature is between -60 deg. C and room temperature" and "the temperature is between room temperature and the glass transition temperature" respectively; these limitations does not further limit the independent claim 76 wherein the temperature is below room temperature.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 76-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hijlkema et al. (U.S Pub. No. 20020143382) in view of Pacetti (U.S Patent No. 6574497) and further in view of Rosenthal et al. (U.S Pub. No. 2003/0144727).

Regarding claims 76, 81-82 and 83, Hijlkema (Abstract and paragraphs 6 and 28) discloses a method of making a medical device comprising:

providing a stent having a coating comprises a polymer,

positioning the stent on a balloon of a catheter assembly; and

mounting the stent on the balloon with thermal regulation to increase hardness by crimping.

Hijlkema discloses the coating comprises a polymer (paragraph 21) and a polymer can have a Tg below or above ambient temperature depending on the ambient temperature and the temperature of the existing surface of the coating may be either heated or cooled (paragraph 30) but does not expressly discloses the polymer as poly(vinylidene fluoride-co-hexafluoroproylene), it is well known to use a fluorine containing elastomer such as copolymers of chlorotrifluorethylene and vinylidene fluoride to be affixed to a medical device, for purposes such as imaging as evidenced by Pacetti (column 9, lines 5-25). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use poly(vinylidene fluoride-co-hexafluoroproylene) to affix to a medical device as taught by Pacetti.

Although the combination of Hijlkema and Pacetti does not disclose the property of the poly(vinylidene fluoride-co-hexafluoroproylene), it is submitted that poly(vinylidene fluoride-co-hexafluoroproylene) inherently has the claimed properties of glass transition temperature being below room temperature and shore hardness being 60A to 80D or 80A to 60D.

Furthermore, Hijlkema discloses increasing the shore hardness of the polymer but does not expressly disclose the percentage of increase. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation (see In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)). Therefore, it would have been obvious to one

of ordinary skill in the art to perform routine experimentation results in the claimed range of increase in hardness.

Hijlkema discloses the coatings maybe designed to facilitate the acceptance of the stent into its applied surroundings or to enable the delivery of therapeutic to the lumen and its surroundings (paragraph 5), but does not specify the therapeutic is an antiproliferative drug. However, it is well known in medical devices such as stents for delievering a biologically active material to a desired location within the body of a patient wherein the biologically active material includes agents such as antiproliferative as shown by Rosenthal (paragraphs 1 and 121-126). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the well known biologically active agent for the stent of Hijlkema.

Regarding claims 77-80, Hijlkema teaches dependant upon the ambient temperature, the coating's preexisting temperature and the glass transition temperature of the coating, the temperature of the existing surface of the coating may be either heated or cooled (paragraph 30), but does not expressly disclose the specific temperature. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation (see In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)). Therefore, it would have been obvious to one of ordinary skill in the art to perform routine experimentation results in the claimed range of temperature.

Response to Arguments

Applicant's arguments filed 5/18/2009 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant essentially argues that Hijlkema fails to teach "temperature below room temperature" because in a preferred embodiment Hijlkema teaches the temperature approximately 20 deg. C above the glass transition temperature. Upon further consideration, the Examiner found that even in the preferred embodiment of Hijlkema, a temperature of 20 deg. C above the glass transition temperature of a polymer can still be below room temperature. Furthermore, in the general broader teaching of Hijlkema, dependant upon the ambient temperature, the coating's preexisting temperature and the glass transition temperature of the coating, the temperature of the existing surface of the coating may be either heated or cooled. Therefore, Hijlkema suggests cooling the coating to a desired temperature.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PHU H. NGUYEN whose telephone number is (571)272-5931. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Phillip Tucker can be reached on 571-272-1095. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

P.N 8/18/2009

/Philip C Tucker/
Supervisory Patent Examiner, Art Unit 1791

Appendix C

US 20020143382A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2002/0143382 A1**

Hijlkema et al. (43) **Pub. Date: Oct. 3, 2002**

(54) **THERMAL REGULATION OF A COATED WORK-PIECE DURING THE RECONFIGURATION OF THE COATED WORK-PIECE**

(76) Inventors: **Luuk Hijlkema**, Moycullen (IE); **Michael Austin**, Tuam (IE); **Jan Weber**, Tuam (IE)

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(21) Appl. No.: **09/819,638**

(22) Filed: **Mar. 29, 2001**

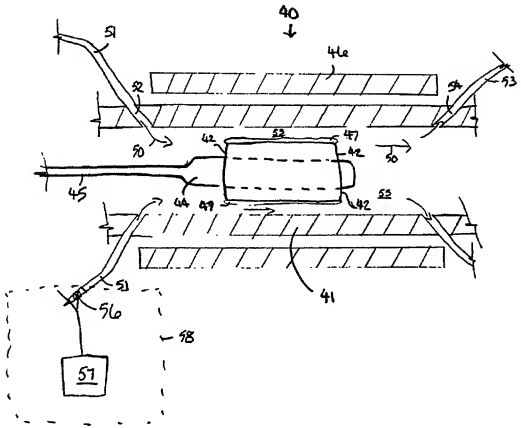
Publication Classification

(51) **Int. Cl.**[7] **A61F 2/06**

(52) **U.S. Cl.** **623/1.11**; 427/2.25

(57) **ABSTRACT**

Thermal regulation of a coated work-piece during the reconfiguration of the work-piece is provided. One method embodying the invention comprises placing an externally coated reconfigurable work-piece, whose hardness has been temporarily modified to resist damage during the reconfiguration of the work-piece, into a reconfiguration chamber of a reconfiguration apparatus and reconfiguring the work-piece from a first configuration to a second configuration via physical communication between the external coating of the reconfigurable work-piece and the reconfiguration apparatus.



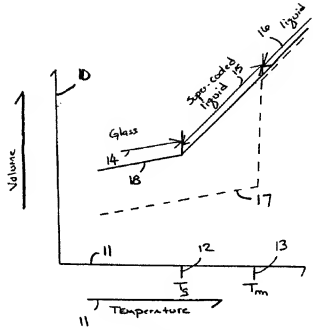


Fig. 1

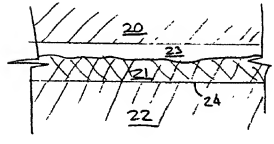


Fig. 2

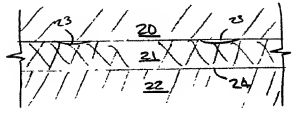


Fig. 3

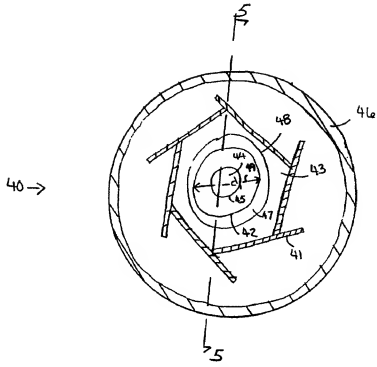

5
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Fig. 4

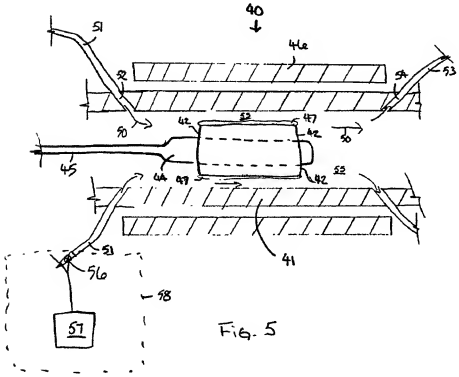
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Fig. 5

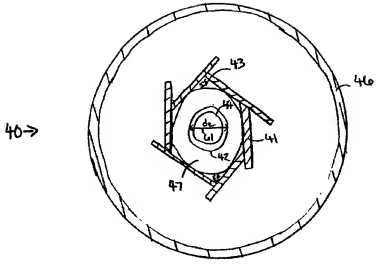

Fig. 6

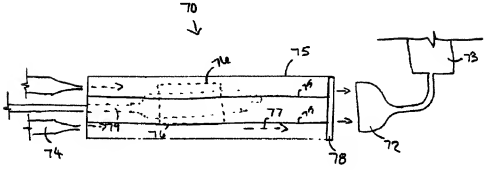

Fig. 7

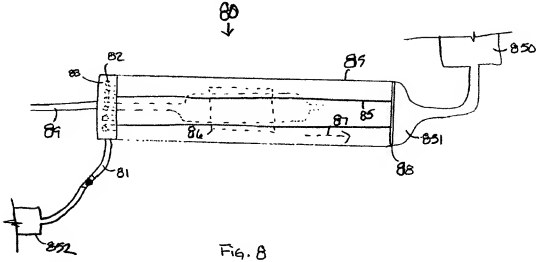

Fig. 8

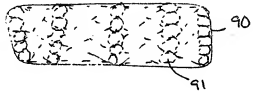

Fig. 9

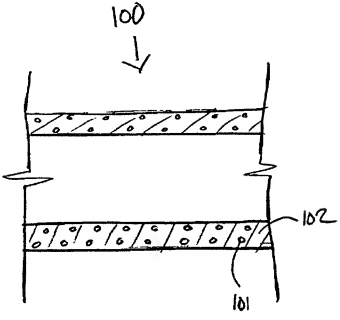

Fig. 10

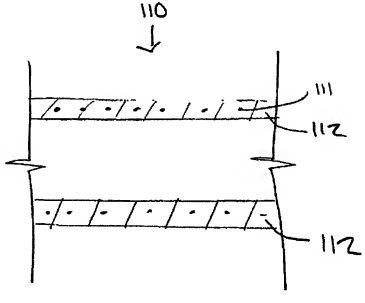

Fig. 11

THERMAL REGULATION OF A COATED WORK-PIECE DURING THE RECONFIGURATION OF THE COATED WORK-PIECE

TECHNICAL BACKGROUND

[0001] The present invention regards protecting a coated work-piece during its manufacture or reconfiguration. More specifically the present invention regards reducing the probability of damaging the coating of a work-piece during the work-piece's manufacture by managing or regulating the temperature of the coating.

BACKGROUND OF THE INVENTION

[0002] Articles of manufacture are regularly coated for numerous and varying reasons. For example, they may be coated to protect them from the intrusive handling they may be subjected to during their manufacture or to protect them from the environmental effects they may endure after they are manufactured. In either of these, as well as in others, damage to the coating, of a work-piece, resulting from the handling or reconfiguration of the work-piece, is an unwanted result.

[0003] When the coating of a work-piece becomes scratched or otherwise damaged during the work-piece's manufacture, the scratches can promote the deterioration of the work-piece by exposing the work-piece's surface to its surroundings. Should the work-piece, upon its completion, be employed in a corrosive environment, the exposed surface of the finished product would be more vulnerable to corrosion than if its coating were completely intact. Moreover, the scratches and inconsistencies in the coating of the work-piece may also reduce the effectiveness of the finished product. For example, should the coating be used to uniformly deliver some type of releasable substance, inconsistencies in the surface of the coating can foster uneven and inconsistent delivery of the releasable substance to the deployed product's final surroundings.

[0004] An expandable coated stent is one specific example of the coated work-pieces described above. Expandable stents are tube-like medical devices designed to support the inner walls of a vessel within the body of a patient. These stents are typically positioned within a targeted lumen of the body and then expanded to provide internal support for the lumen. These stents may be self-expanding or, alternatively, may require external forces to expand them. In either case they are typically deployed through the use of a catheter of some kind. These catheters typically carry the stent at their distal ends. In use, a practitioner will position the catheter's distal end near the target area of the lumen. Once properly positioned the stent will be deployed by the practitioner such that it comes to rest near or in direct contact with the inner walls of the lumen. There, the stent will remain to provide support for the lumen.

[0005] Due to the interaction of the stent with the inner walls of the lumen, stents have been coated to enhance their effectiveness. These coatings may, among other things, be designed to facilitate the acceptance of the stent into its applied surroundings or to enable the delivery of therapeutic to the lumen and its surroundings. Thus, when the coating is haphazardly applied or has somehow been removed during the stent's manufacture, both the stent's longevity and its effectiveness can be reduced.

[0006] The coatings on the stent may be applied at various times during its life cycle including its manufacture, its placement onto the distal end of the delivery catheter, and contemporaneous with the medical procedure. At each of these times the coating may be at risk of being scratched, damaged or otherwise removed from the surface of the stent. For example, during their manufacture, stents are often crimped onto the distal end of a delivery catheter. This crimping process requires the exertion of significant forces against the coating of the stent to facilitate a reduction in the stent's circumference to secure it to the catheter. During this crimping, the mechanical arms of a crimper may come in contact with the coating of the stent as they reduce the diameter of the stent. This compressive contact can scratch, indent, wipe-off or otherwise breach the integrity of the coating—an undesirable result.

SUMMARY OF THE INVENTION

[0007] Thermal regulation of a coated work-piece during the reconfiguration of the work-piece is provided. One method embodying the invention comprises placing an externally coated reconfigurable work-piece, whose hardness has been temporarily modified to resist damage during the reconfiguration of the work-piece, into a reconfiguration chamber of a reconfiguration apparatus and reconfiguring the work-piece from a first configuration to a second configuration via physical communication between the external coating of the reconfigurable work-piece and the reconfiguration apparatus.

[0008] An apparatus embodying the invention includes a reconfiguration chamber, a nozzle in fluid communication with the reconfiguration chamber, a regulator in fluid communication with the nozzle, the regulator adapted to regulate the flow of a thermal transfer fluid, and a controller in communication with the regulator. Wherein the controller is adapted to send control signals to the regulator to maintain the surface temperature of the external coating of the reconfigurable work-piece within a predetermined temperature range and wherein the predetermined temperature range affords a predetermined minimum hardness for the external coating of the reconfigurable work-piece.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] **FIG. 1** is a graph of volume versus temperature for an exemplary polymer coating.

[0010] **FIG. 2** is an enlarged partial side cross-sectional view of a reconfiguration chamber and a reconfigurable coated work-piece prior to the reconfiguration of the coated work-piece in accord with an embodiment of the present invention.

[0011] **FIG. 3** is the view of **FIG. 2** shown during the reconfiguration of the coated work-piece in accord with an embodiment of the present invention.

[0012] **FIG. 4** is a cross-sectional view of a reconfiguration chamber shown prior to the execution of a work stroke in accord with an alternative embodiment of the present invention.

[0013] **FIG. 5** is a sectional view taken along line **5-5** of **FIG. 4**.

[0014] **FIG. 6** is another cross-sectional view of the reconfiguration chamber of **FIG. 4** shown after a work stroke has been completed in accord with an alternative embodiment of the present invention.

[0015] **FIG. 7** is a side view of a reconfiguration chamber in accord with another alternative embodiment of the present invention.

[0016] **FIG. 8** is a side view of a reconfiguration chamber in accord with another alternative embodiment of the present invention.

[0017] **FIG. 9** is a side view of a self-expanding stent within a sheath as manufactured by a method in accord with another alternative embodiment of the present invention.

[0018] **FIG. 10** is an enlarged side cross-sectional view of a reconfiguration chamber in accord with another alternative embodiment of the present invention.

[0019] **FIG. 11** is an enlarged side cross-sectional view of a reconfiguration chamber in accord with another alternative embodiment of the present invention.

DETAILED DESCRIPTION

[0020] In one embodiment of the present invention the hardness or resilience of the coating of a work-piece is temporarily increased by adjusting its preexisting temperature to be closer to its glass transition temperature. Then, while the coating is in this temporarily hardened or more resilient state, the force required to reconfigure the work-piece is applied against the coating. By temporarily increasing the hardness of the coating through its change in temperature, the coating is better able to withstand the forces and pressures exerted upon it during the reconfiguration of the work-piece. Thus, the coating is more likely to remain intact both during the remainder of the manufacturing of the work-piece and after the work-piece has been completely manufactured and is employed for its intended purpose.

[0021] **FIG. 1** is a graph of volume versus temperature for a polymer that may be used as a coating in accord with one embodiment of the present invention. The temperature of the polymer is plotted along the x-axis **11** while its corresponding volume is plotted along the y-axis **10**. The glass transition temperature (T_g) **12** as well as the melting temperature (T_m) **13** are specifically labeled on the x-axis **11** of the graph. Also labeled in the graph is the line **18** representing the specific volume for a given temperature of this exemplary polymer. This line **18** has three phase ranges identified on it, the glass phase **14**, the super-cooled liquid phase **15**, and the liquid phase **16**. The crystalline property delineation line **17** for this exemplary polymer is also evident in **FIG. 1**.

[0022] The exemplary polymer graphed in **FIG. 1** is a typical polymer. It is comprised of chains or strings of molecules that are interwoven and able to move in and around one another. As the polymer cools the chains loose their ability to freely flow around and among one another, and, thus, the polymer becomes stiffer and decreases in volume.

[0023] When the polymer temperature is within the liquid range **16** the chains of molecules comprising the polymer may move freely amongst one another and, consequently, the polymer behaves much like a liquid. As the temperature decreases, the thermal agitation among the molecules lessens and the volume of the liquid shrinks. This decrease in volume continues below the melting point (T_m) **13** of the polymer and into its super-cooled liquid range. Below the melting point (T_m) **13**, the chains of molecules may still flow around and among themselves but they do so at a lower rate than in the liquid phase. It is here, in this super-cooled liquid range, that the hardness and resiliency of the polymer will increase as its temperature approaches the glass transition temperature (T_g) **12**. When the temperature of the polymer reaches the glass transition temperature (T_g) **12** the polymer enters the glass phase **14**. Here, the polymer becomes more brittle than in the super-cooled liquid phase as the molecules can no longer continually rearrange themselves. Moreover, as is evident in the graph of **FIG. 1**, the rate of volume change in relation to temperature changes at this point as it is one constant above the glass transition temperature (T_g) **12** and a different constant below the glass transition temperature (T_g) **12**.

[0024] **FIG. 2** provides an enlarged partial cross-section of a slidable outer wall **20** of a reconfiguration chamber positioned near a reconfigurable work-piece **22**, prior to a work stroke, in accord with one embodiment of the present invention. In this embodiment, prior to the beginning of a work stroke, the slidable outer wall is not in contact with the coating **21** or the reconfigurable work-piece **22** as is evident by the existence of void **23**.

[0025] **FIG. 3** provides an enlarged cross-section of the slidable outer wall **20** and the reconfigurable work-piece **22** of **FIG. 2** during a work stroke. As can be seen, the slidable outer wall **20** is in direct contact with the coating **21** of the reconfigurable work-piece **22**. As is also evident, most but not all of the void **23** is filled during the work stroke as some small areas of void **23** remain when the slidable outer wall **22** comes in contact with the coating.

[0026] In order to increase the resiliency and hardness of the coating and to reduce the potential damage to it from the direct contact with the slidable outer wall **20**, the coating may be cooled to be within its super-cooled liquid range. By lowering the temperature of the coating **21**, closer to the glass transition temperature of the coating, the coating **21** can be sufficiently hardened to protect it from the forces generated by its direct contact with the slidable outer wall **20**. Due to this temporal hardening, the coating **21** may remain substantially intact on the work-piece and may be able to continue to protect the work-piece **22** during the remaining steps of its manufacture and, afterwards, as the work-piece is deployed for its intended use.

[0027] The slidable outer wall **20** provided in FIGS. **2-3** may be any one of innumerable pinching, moving, or force exerting components of a manufacturing machine or process. Likewise, the reconfigurable work-piece may be any one of innumerable work-pieces or products of manufacture currently manufactured in modern manufacturing systems. In addition, the coating **21** may be one of numerous commercial or industrial coatings including various ceramics, polymers, and waxes. These polymers could include SIBS polymers (styrene-isobutylene-styrene) and any other suitable polymer.

[0028] **FIG. 4** is a cross-sectional view of a reconfiguration chamber **40** as may be used to crimp or crease a stent **42** onto the distal end of a balloon catheter **44** in accordance with an alternative embodiment of the present invention. As can be seen in **FIG. 4**, the reconfiguration chamber **40** has slidable outer walls **41** that are in physical communication with one another and define a hexagonal-like adjustable aperture. Resident within this aperture is the distal end of a

balloon catheter **44** having an exterior wall **45**. A stent **42**, encircling the distal end of the balloon catheter **44** and having a coating **47** with an exterior surface of the coating **48**, is also pictured in **FIG. 4**. As can also be seen in this embodiment, the exterior surface of the coating **48** has a void **43** between it and the interior faces of the slidable outer walls **41**. This void **43** may exist both before and after the completion of a work stroke of the slidable outer walls **41**. The initial diameter of the stent **42**, prior to the completion of a work stroke, is indicated with the character d_1 and the numeral **49**.

[0029] In this embodiment, the slidable outer walls **41** of the reconfiguration chamber **40** are activated to crimp the stent **42** onto the balloon catheter **44**. When activated, the slidable outer walls **41** slide towards one another and, thus, reduce the size of the aperture defined by them. As the aperture's diameter reaches the size of the exterior surface **48** of the coating **47**, pressure is begun to be exerted on the coating **47** of the stent **42** and the stent begins to be reconfigured. As the diameter of the aperture is further reduced so too is the cross-sectional diameter of the stent **42**. In order to retard damage to the coating **47** that contacts the slidable outer walls **41**, the temperature of the coating **47** has been adjusted either before placing the stent **42** into the reconfiguration chamber **40** or while the stent **42** is located within the reconfiguration chamber **40**.

[0030] In this embodiment the temperature of the coating **47** is adjusted after the stent has been placed within the reconfiguration chamber **40**. Here, a thermally conductive fluid may be flushed through the void **43** and in contact with the coating **47** to adjust the coating's temperature. Dependant upon the ambient temperature, the coating's preexisting temperature, and the glass transition temperature of the coating, the temperature of the existing surface of the coating **47** may be either heated or cooled. In this embodiment the temperature of the coating is reduced through the introduction of cooled ultra-dry air into the void **43** until the desired resultant temperature of the coating **47** is achieved. Other cooling mediums may also be used including both compressible and non-compressible fluids. The desired resultant temperature may depend upon the glass transition temperature of the coating, the structural rigidity of the stent, the properties of the balloon catheter, and the anticipated future handling of the stent. The desired temperature or temperature range may be a percentage of the T_g or it may be a specific range of quantified values. In this embodiment, the desired temperature range is approximately 20° Celsius above the glass transition temperature of the coating.

[0031] In this embodiment, once the temperature of the coating has been adjusted to be within the desired temperature range, the slidable outer walls **41** may complete a work stroke by sliding inwardly and, consequently, reconfiguring the stent **42** from a first position having a diameter d_1 to a second position having a diameter d_2 (illustrated in **FIG. 6**).

[0032] An insulating tube **46** is positioned around the slidable outer walls **41** and is clearly evident in **FIG. 4**. This insulating tube **46** provides additional thermal buffering between the potentially extreme temperatures generated within the reconfiguration chamber and its surroundings. The insulating tube **46** may be made from an insulating ceramic or any other suitable insulating material. The slidable outer walls **41** may also be designed to provide buffering between the extreme temperatures generated within the reconfiguration chamber and the surroundings. For example the slidable outer walls **41** may be made from materials such as Dupont™ Delrin™ (acetal homopolymer and copolymer) and Zirconium oxide ceramic which has been partially stabilized with Yttria to provide supplementary thermal buffering between the work-piece and the surrounding area.

[0033] **FIG. 5** is a side cross-sectional view taken along line **5-5** of the reconfiguration chamber **40** of **FIG. 4**. Various features of the reconfiguration tube **40** are evident in this illustration including the entrance tube **51**, the exit tube **53**, nozzles **52** and **54**, insulating tube **46**, coating **47**, thermal transfer fluid flow arrows **50**, thermal transfer fluid **55**, stent **42**, slidable outer walls **41**, balloon catheter exterior surface **45**, balloon catheter **44**, regulator **56**, and controller **57**.

[0034] After the distal end of the catheter **44** has been placed within the reconfiguration chamber **40**, in order to adjust the temperature of the coating **47**, thermal transfer fluid **53** may be delivered through tube **51** and nozzle **52** into direct contact with the coating **47**. Then, after passing over the coated stent, the fluid **50** may be recaptured through nozzles **54** and exit tubes **53** where it can be stored or recycled back into the process. The thermal transfer fluid **55** may be introduced and circulated both prior to and during the reconfiguration of the stent **42**, although it is preferable that the flow of the thermal transfer fluid **55** be halted once the slidable outer walls **41** have begun to move. The thermal transfer fluid may be any one of numerous suitable fluids, including liquid nitrogen, water, liquid helium, dry air, nitrogen, helium, or any other suitable compressible and non-compressible fluids.

[0035] After the crimping has occurred the slidable outer wall **41** may open and the thermal transfer fluid **55** may cease its flow through the chamber. The balloon catheter **44** may then be removed from the reconfiguration chamber **40** and its temperature permitted to return to the ambient temperature. Alternatively, the distal end of the catheter **44**, carrying the now crimped stent **42**, may be subjected to other manufacturing steps that may also benefit from the coating's temporally increased hardness.

[0036] In this embodiment the regulator **56** and controller **57** act together as a means for adjusting and maintaining the temperature of the coating **58** although other configurations for this means are plausible. These components work together to adjust and maintain the temperature of the coating **47**. The amount of fluid flowing through the entrance nozzles **52** into the reconfiguration chamber may be monitored by the controller **57**. When the requisite flow is detected no action may be required. However, should the controller **57** determine that the rate of fluid flow should be adjusted, in order to adjust or maintain the temperature of the coating **47**, it may, as required, send a signal that opens or closes the regulator **56**.

[0037] This means for adjusting and maintaining the temperature **58** can take numerous other configurations. For example, while it is illustrated as being comprised of regulators and controllers regulating the flow of fluid into the reconfiguration chamber, this means could, instead, comprise manually adjustable valves that are adjusted by an operator monitoring the temperature of the coating. Alter-

natively, this means could also be electrical coils or hollow thermal conduction tubes carrying a thermal conductive fluid such as liquid nitrogen. The coils in either case may be placed within the slidable outer walls **41** and may be used to provide the thermal adjustment of the coating of the stent via the regulation of the fluid or electrical current flowing through them.

[0038] **FIG. 6** provides an enlarged cross-sectional view of the reconfiguration chamber during a work stroke. As can be seen in **FIG. 6** the slidable outer walls **41**, containing residual transfer fluid **55** in the voids **43**, have closed in on themselves and have reconfigured the stent **42** into a second position such that the diameter d_2 of the stent **42** is smaller than the diameter d_1 of the stent **42** in **FIG. 4**. Because the temperature of the coating was brought closer to its glass transition temperature, the coating has substantially retained its shape, has not been substantially damaged, and has adequately transferred the forces generated from the slidable outer walls to the stent **42**.

[0039] **FIG. 7** shows a side view of a reconfiguration chamber in accord with another alternative embodiment of the present invention. In **FIG. 7**, nozzle **74**, catheter **79**, stent **76**, flow arrow **77**, thermocouple **78**, slidable outer walls **75**, uptake **72**, and thermal transfer fluid storage chamber **73** are all clearly evident. In this embodiment, after placing the distal end of the catheter into the reconfiguration chamber, the nozzle **74** may be used to inject thermal transfer fluid into the reconfiguration chamber **70** in order to adjust the temperature of the coating resident on stent **76**. In this embodiment, the thermocouple **78** may be used to monitor the temperature of the thermal transfer fluid leaving the reconfiguration chamber such that the stent resident within the reconfiguration chamber **70** may be adjusted to a desired target temperature. In this embodiment, the uptake **72** may be positioned near the exit of the reconfiguration chamber **70** and may be used to capture thermal transfer fluid leaving the reconfiguration chamber in a thermal transfer fluid storage chamber **73** for subsequent disposal or reuse.

[0040] Although not illustrated in this figure, the thermocouple **78** may be in communication with a controller to act in conjunction with it as a means for adjusting and maintaining the temperature of the coating.

[0041] **FIG. 8** is a side view of an alternative reconfiguration chamber in accord with another alternative embodiment of the present invention. Illustrated in **FIG. 8** are thermal transfer fluid storage chambers **850** and **852**, entrance tube **81**, couple ring **83**, catheter **89**, nozzles **82**, stent or work-piece **86**, fluid flow arrows **87**, slidable outer walls **85**, thermocouple **88**, and uptake **851**. While similar to the embodiment in **FIG. 7**, the embodiment of **FIG. 8** utilizes a couple ring **83** in fluid communication with numerous nozzles **82** that travel through the slidable outer walls **85**. These nozzles direct the thermal transfer fluid into the reconfiguration chamber and may be designed to increase or decrease the velocity of the fluid's flow in relation to its velocity in the tube **81**. By increasing or decreasing the flow of the fluid, the thermal transfer rate between the fluid and the coating can be concomitantly increased or decreased.

[0042] While several of the above embodiments describe a balloon expandable stent, self-expanding stents may also be crimped in accord with the processes described above. These self-expanding stents, rather than requiring the forces generated by the balloon catheter to expand them, are capable of expanding under their own power once they have been deployed. In **FIG. 9**, as can be seen, the stent, previously crimped by the processes described above to fit inside the sheath **90**, may be stored within the sheath **90**, where it will remain until it is deployed at a target site of the body. Upon being deployed, the sheath **90** may be removed thereby allowing the stent **91** to expand under its own forces.

[0043] As described above and as shown in **FIGS. 10** and **11**, the slidable outer walls may contain conduits or lines for adjusting the temperature of the coating.

[0044] In **FIG. 10**, which is a side sectional view of reconfiguration chamber **100**, the slidable outer walls **102** are shown with fluid conduits **101**. These fluid conduits may be looped and travel throughout the individual slidable outer walls and may contain a thermal transfer fluid to adjust the temperature of the slidable outer wall **102**. This fluid may be cooled air and may be pumped through the conduits by a pumping system (not shown).

[0045] **FIG. 11** is a side sectional view of a reconfiguration chamber **110**. Rather than providing for a fluid conduit as in **FIG. 10**, the slidable outer walls **112** in **FIG. 11** contain electrical lines **111**. These electrical lines, like the conduits described above, may be used to raise the temperature of the coating rather than lower it to reach the desired resiliency or, alternatively, may be used to thaw the coating after the stent has been reconfigured and prior to its ejection from the reconfiguration chamber **110**.

[0046] These conduits or lines may be used in place of the thermal fluid transfer methods described above or in addition to the thermal fluid transfer methods described above. In other words, the conduits or lines placed into the walls **102** and **112** may be the sole source of adjusting the temperature of the coating or they may be a supplement to thermal transfer fluid being pumped over the coating. These conduits and lines may also be classified as a means for adjusting and maintaining the temperature of the coating.

[0047] Thermal conditioning of a coated work-piece during the reconfiguration of the work-piece is provided. While various embodiments have been conveyed, it will be evident to one of skill in the art that other embodiments, also within the spirit and scope of the present invention, are plausible.

What is claimed is:

1. A method of protecting the external coating on an externally coated reconfigurable work-piece during the reconfiguration of the work-piece in a reconfiguration apparatus comprising:

placing the externally coated reconfigurable work-piece into a reconfiguration chamber of the reconfiguration apparatus, the hardness of the external coating being temporarily modified to resist damage during the reconfiguration of the work-piece; and

reconfiguring the work-piece from a first configuration to a second configuration via physical communication between the external coating of the reconfigurable work-piece and the reconfiguration apparatus.

2. The method of claim 1 further comprising:

adjusting the temperature of at least a portion of the coating of the work-piece to be within the coating's super cooled liquid temperature range.

3. The method of claim 2 wherein adjusting the temperature of at least a portion of the coating includes placing a thermal transfer fluid in thermal communication with the external coating of the reconfigurable work-piece.

4. The method of claim 2 further comprising:

raising the temperature of the external coating after the work-piece has been reconfigured.

5. The method of claim 3 wherein the thermal transfer fluid is a non-compressible fluid.

6. The method of claim 3 wherein the thermal transfer fluid is a compressible fluid.

7. The method of claim 1 wherein the reconfiguration of the work-piece is caused by movement of moveable pieces of the reconfiguration chamber.

8. The method of claim 1 wherein the reconfiguration of the work-piece is caused by the contact of a plurality of blades against the coating of the work-piece, the blades moveable within the reconfiguration apparatus from a first position to a second position.

9. The method of claim 8 wherein the plurality of blades define the reconfiguration chamber, the reconfiguration chamber having a variable internal volume.

10. The method of claim 1 wherein the reconfigurable work-piece is either a coated stent, a coated graft, a coated stent graft or a coated vena cava filter.

11. The method of claim 2 wherein the temperature of the coating is adjusted to be at least 10 degrees Celsius closer to its glass transition temperature.

12. The method of claim 2 wherein the temperature of the coating is adjusted to be at least 20 degrees Celsius closer to its glass transition temperature.

13. The method of claim 1 wherein the reconfigurable work-piece, in its second configuration, is crimped onto a carrier device.

14. The method of claim 13 wherein the reconfigurable work-piece is a stent and the carrier device is an expandable delivery balloon.

15. The method of claim 1 further comprising:

placing the reconfigurable work-piece into a sheath after reconfiguring the work-piece via physical communication between the external coating and the reconfiguration chamber apparatus.

16. The method of claim 15 wherein the reconfigurable work-piece is a self-expanding stent.

17. An apparatus for reconfiguring from a first configuration to a second configuration an externally coated work-piece comprising:

a tubular reconfiguration chamber having a plurality of slidably mounted outer walls, the outer walls slidably mounted along individual radial lines emanating from and orthogonal to the central longitudinal axis of the tubular reconfiguration chamber; and

a means for adjusting and maintaining the temperature of the external coating of a work-piece located within the tubular reconfiguration chamber.

18. The apparatus of claim 17 wherein the means for adjusting and maintaining the temperature includes a fluid ejection nozzle in fluid communication with the tubular reconfiguration chamber.

19. The apparatus of claim 17 wherein the means for adjusting and maintaining the temperature is adapted to lower the temperature of the external coating to be within the coating's super-cooled liquid temperature range.

20. The apparatus of claim 17 wherein the means for adjusting and maintaining the temperature is adapted to raise the temperature of the external coating from its preexisting temperature to be within the coating's super-cooled liquid temperaturc range.

21. The apparatus of claim 17 wherein the tubular reconfiguration chamber has a polygonal cross-section.

22. An apparatus for reconfiguring an externally coated reconfigurable work-piece comprising:

a reconfiguration chamber;

a nozzle in fluid communication with the reconfiguration chamber;

a regulator in fluid communication with the nozzle, the regulator adapted to regulate the flow of a thermal transfer fluid exiting the nozzle; and

a controller in communication with the regulator, the controller adapted to send control signals to the regulator to maintain the surface temperature of the external coating of the reconfigurable work-piece within a predetermined temperature range, the predetermined temperature range associated with a predetermined minimum hardness of the external coating of the reconfigurable work-piece.

23. The apparatus of claim 22 wherein the controller is further adapted to send control signals to the regulator to modify the surface temperature of the external coating of the reconfigurable work-piece to be at least 20 degrees Celsius closer to the external coating's glass transition temperature.

24. The apparatus of claim 22 wherein the controller is further adapted to send control signals to the regulator to modify the surface temperature of the external coating of the reconfigurable work-piece to be at least 10 degrees Celsius closer to the external coating's glass transition temperature.

25. The apparatus of claim 22 wherein the reconfiguration chamber has a polygonal cross-section.

26. The apparatus of claim 22 wherein the nozzle is incorporated into a wall of the reconfiguration chamber and wherein the nozzle is in fluid communication with a thermal transfer fluid storage chamber.

* * * * *

Appendix D

US006574497B1

(12) **United States Patent**
Pacetti

(10) **Patent No.: US 6,574,497 B1**
(45) **Date of Patent: Jun. 3, 2003**

(54) **MRI MEDICAL DEVICE MARKERS UTILIZING FLUORINE-19**

(75) Inventor: **Stephen Dirk Pacetti**, San Jose, CA (US)

(73) Assignee: **Advanced Cardiovascular Systems, Inc.**, Santa Clara, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 187 days.

(21) Appl. No.: **09/746,843**

(22) Filed: **Dec. 22, 2000**

(51) **Int. Cl.**[7] **A61M 25/00**

(52) **U.S. Cl.** **600/420**; 600/435; 606/200

(58) **Field of Search** 600/420, 431, 600/433, 435; 606/200

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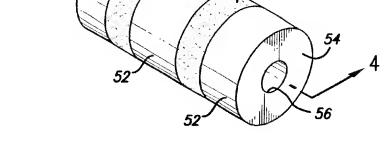
Primary Examiner—Kevin Lee
(74) *Attorney, Agent, or Firm*—Fulwider Patton Lee & Utecht, LLP

(57) **ABSTRACT**

Medical devices that incorporate compounds containing fluorine-19 materials for use as contrast agents and passive markers in interventional magnetic resonance angiography. The device may be a guidewire, guiding catheter, angioplasty catheter, stent, embolic protection device, endovascular graft, endotracheal tube, Foley catheter, Hickman catheter, Broviac catheter, cerebrospinal fluid shunt, biliary stent, stylet, biopsy needle, electrode, percutaneous or endoluminal transducer or other desired interventional medical device. The fluorine-19 material may be configured from an elastomer, a fluid, a fluorosilicone, or a perfluorocarbon grease or oil. Such materials may be incorporated into marker bands and/or stripes, or may be deposited into or dispersed within the walls or lumens of the medical device to be visualized. Use of fluorine-19 containing markers and contrast agents provide a novel method of performing angioplasty and deploying stents, grafts, embolic protection and other such devices using interventional magnetic resonance angiography.

46 Claims, 9 Drawing Sheets



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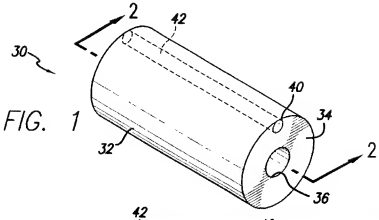
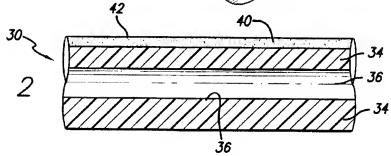


FIG. 1



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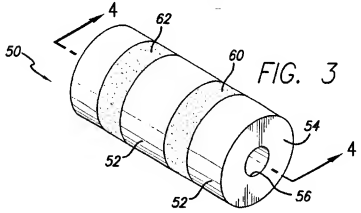

FIG. 3

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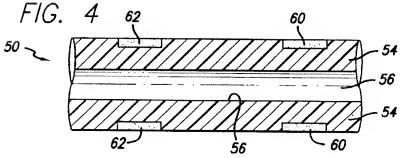

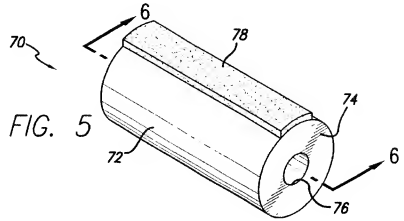

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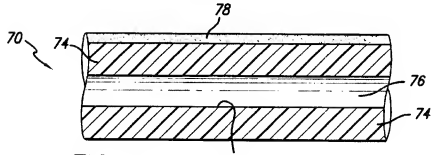

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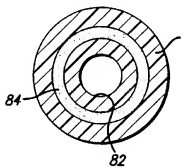

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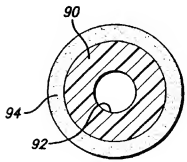

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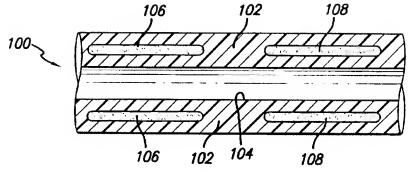

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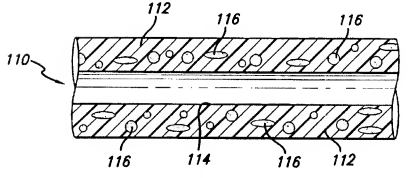

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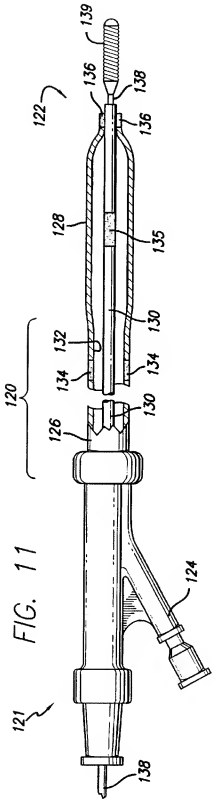
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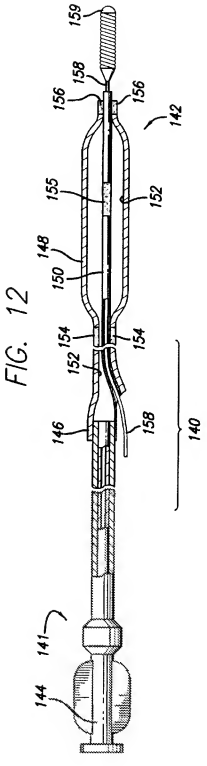
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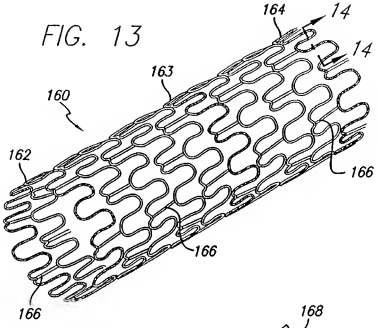
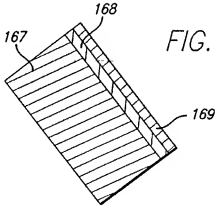
FIG. 12

FIG. 13





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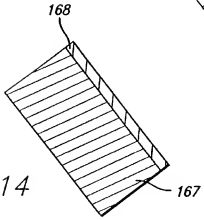

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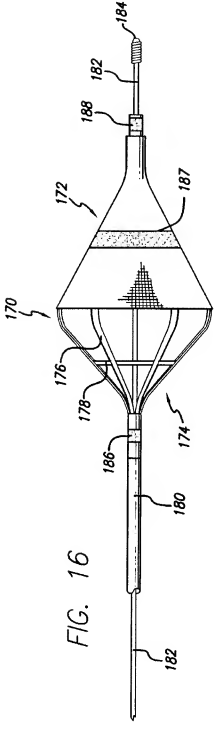
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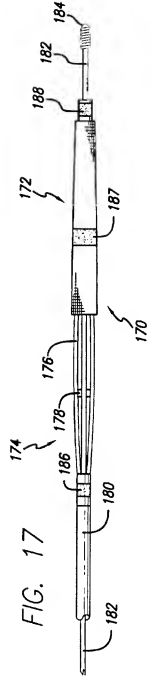
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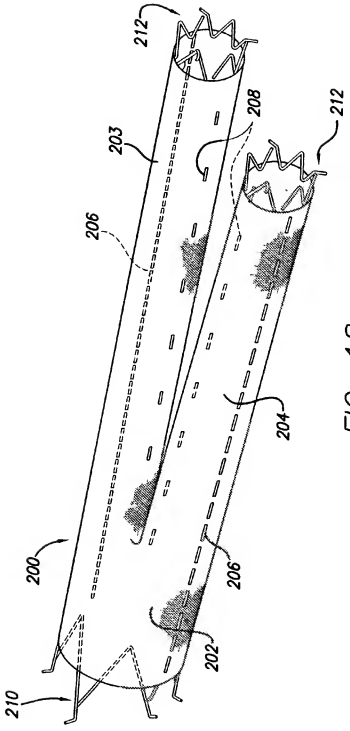
FIG. 17



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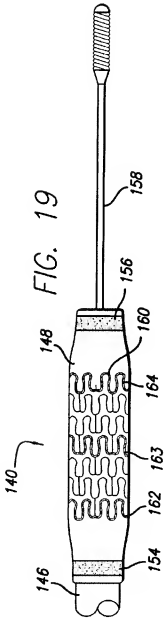
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FIG. 19

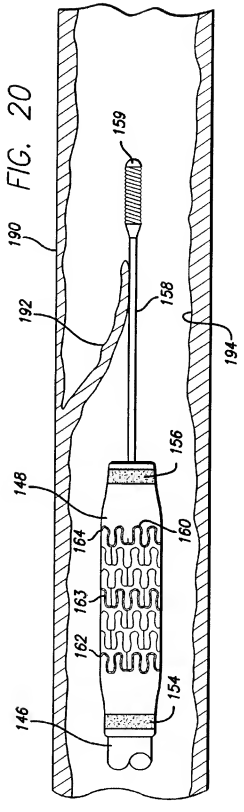
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FIG. 20

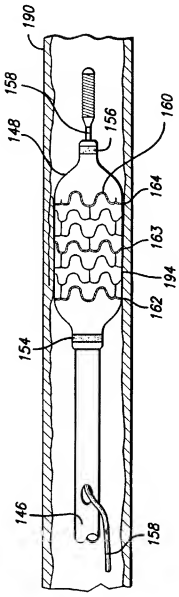

FIG. 21

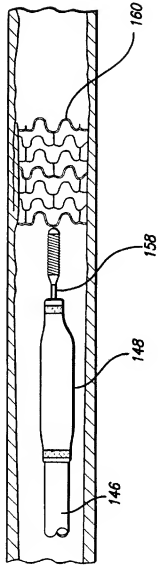

FIG. 22

MRI MEDICAL DEVICE MARKERS UTILIZING FLUORINE-19

BACKGROUND OF THE INVENTION

The present invention relates to apparatus and methods for medical imaging, specifically to the use of passive markers for magnetic resonance imaging. In a particular, the invention relates to the use of fluorine-19 (^{19}F) nuclei containing compounds as contrast agents and markers for medical devices used in interventional magnetic resonance angiography.

Currently, x-ray fluoroscopy is the preferred imaging modality for cardiovascular interventional procedures. No other method, at this time, has the temporal or spatial resolution of fluoroscopy. As good as fluoroscopy is, however, it does have drawbacks. Catheterization is required in order to directly inject the high concentration of iodinated contrast agent required. Systemic administration of the contrast agent would require too high a dose of agent. Additionally, iodinated contrast agents are nephrotoxic with a real incidence of acute renal failure, particularly in patients with compromised renal function. Allergic reactivity also serves as a contraindication for certain patients. Visualization and tracking of devices under fluoroscopy is accomplished either by the device's inherent adsorption of x-rays, or by the placement of radiopaque markers. Fluoroscopy generates a compressed, two dimensional image of what are three dimensional structures. This requires multiple views to appraise complex vasculature. Moreover, fluoroscopy uses ionizing x-ray radiation with its attendant hazards. This is an issue for the patient during protracted or repeated interventions. It is a daily issue for the interventionalist who must also cope with the burden of personal dose monitoring and wearing lead shielding.

One imaging modality, which has the potential to supplant fluoroscopy, or perhaps replace it in the long term, is magnetic resonance imaging (MRI). MRI does not use ionizing radiation and does not require catheterization to image vasculature. MRI contrast agents, which are often necessary for best resolution, are much less nephrotoxic than iodinated fluoroscopy agents and are effective when administered intravenously.

One advantage of MRI is that different scanning planes and slice thicknesses can be selected without loss of resolution. This selection permits high quality transverse, coronal and sagittal images to be obtained directly. MRI has greater soft tissue contrast and tissue discrimination than computed tomography (CT) or other x-ray based imaging modalities, such as angiography. The reason for this being that in CT, the x-ray attenuation of tissues determines image contrast, whereas in MRI at least four separate variables can determine MRI signal intensity: (i) spin-lattice (longitudinal) relaxation time—T_1, (ii) spin-spin (transverse) relaxation time—T_2, (iii) proton density, and (iv) flow. MRI is presently used for diagnostic applications, but interventional magnetic resonance (iMR) angiography is an active area of research. For example, MRI guided balloon angioplasty has been performed to demonstrate feasibility. Similarly, stent placement in humans under MRI has also been demonstrated.

The technique of MRI encompasses the detection of certain atomic nuclei (those possessing magnetic dipole moments) utilizing magnetic fields and radio-frequency radiation. It is similar in some respects to x-ray computed tomography in providing a cross-sectional display of the body organ anatomy, only with excellent resolution of soft tissue detail. In its current use, the images constitute a distribution map of protons, and their properties, in organs and tissues. However, unlike x-ray computer tomography, MRI does not use ionizing radiation. The fundamental lack of any known hazard associated with the level of the magnetic and radio-frequency fields that are employed renders it possible to make repeated scans on vulnerable individuals. Additionally, any scan plane can readily be selected, including transverse, coronal, and sagittal sections. MRI is, therefore, a safe non-invasive technique for medical imaging.

The hydrogen atom, having a nucleus consisting of a single unpaired proton, has one of the strongest magnetic dipole moments of nuclei found in biological tissues. Since hydrogen occurs in both water and lipids, it is abundant in the human body. Therefore, MRI is most commonly used to produce images based upon the distribution density of protons and/or the relaxation times of protons in organs and tissues. Other nuclei having a net magnetic dipole moment also exhibit a nuclear magnetic resonance phenomenon which may be used in MRI applications. Such nuclei include carbon-13 (six protons and seven neutrons), fluorine-19 (9 protons and 10 neutrons), sodium-23 (11 protons and 12 neutrons), and phosphorus-31 (15 protons and 16 neutrons).

Fluoroscopy uses contrast agents to enhance the imaging of otherwise radiolucent tissues. Not surprisingly, fluoroscopic contrast agents work by x-ray absorption. Contrast agents also exist for MRI image enhancement. They work in a different manner, and typically shorten either the T_1 or T_2 proton relaxation times, giving rise to intensity enhancement in appropriately weighted images. The most popular MRI contrast materials are T_1 shortening agents and, in general, paramagnetic ions of elements with an atomic number of 21 to 29, 42 to 44 and 58 to 70 have been found effective as MRI contrasting agents. Such suitable ions include chromium(III), manganese(II), iron(III), iron (II), cobalt (II), nickel (II), copper (II), prasecodymium(III), neodymium(III), samarium(III) and ytterbium(III). Because of their very strong magnetic moments, gadolinium(III), terbium(III), dysprosium(III), holmium(lll) and erbium(lll) are preferred. Gadolinium(III) ions have been particularly preferred as MRI contrast agents.

In an MRI experiment, the nuclei under study in a sample (e.g. protons, ^{19}F, etc.) are irradiated with the appropriate radio-frequency (RF) energy in a controlled gradient magnetic field. These nuclei, as they relax, subsequently emit RF energy at a sharp resonance frequency. The resonance frequency of the nuclei depends on the applied magnetic field. In some cases, the concentration of nuclei to be measured is not sufficiently high to produce a detectable magnetic resonance signal. Signal sensitivity may be improved by administering higher concentrations of the target nuclei or by coupling the nuclei to a suitable "probe" which will concentrate in the body tissues of interest.

As noted above, iMR angiography is an active area of research. Device tracking and visualization under MRI is necessary for MRI guided interventions. Plastic devices show up poorly under MRI. The reason is that even though the majority of polymers contain hydrogen nuclei, the resonance signals from protons in polymers are broad and chemically shifted from protons in water from which the majority of the MRI signal is derived. Polymeric catheters, for example, show up as regions of little or no signal under MRI (signal voids). Hence, there is a need for markers to track and visualize interventional devices.

MRI markers are divided into two categories, active and passive. Active markers, as the name implies, participate in

the radio frequency signal transmission or reception of the scanner. This includes markers that emit an RF signal, markers that receive an RF signal and convey it to the scanner via a connection, and markers that generate their own magnetic or electrical field by application of electrical currents. The term active implies some sort of electrical circuit is involved. Conversely, passive markers use no wires or circuitry and work by several mechanisms. One scheme is to distort the magnetic field of the scanner. Another is by enhancing or modifying the signal from protons in the vicinity. Still another is by containing nuclei with their own distinct signal that is different from water or fat. Passive markers have the advantage that they are simpler and, generally, have fewer parts. They require no connection to the scanner or additional circuitry. There also may be the perception amongst physicians that active currents and voltages in or on interventional devices create additional safety issues to be managed. Lastly, passive markers are conceptually similar to the radiopaque markers in fluoroscopy, even if they work in a very different way.

There are two main types of passive markers being proposed. One is based on magnetic susceptibility. This usually includes paramagnetic or ferromagnetic particles, bands, or other components placed in or on the device. These materials perturb the magnetic field in the vicinity of the device. This alters the resonance condition of protons in the vicinity. The net result is a signal void that appears black in MRI images.

The second scheme uses the currently approved gadolinium contrast agents; however, the contrast agents are placed inside the device. For example, gadolinium contrast solution is used to fill the lumen of a catheter or inflate an angioplasty balloon. In T_1 weighted images, aqueous solutions of gadolinium show a signal enhancement due to the T_1 shortening effect of the gadolinium. Gadolinium also shortens T_2 and gives some enhancement in those images as well. In contrast to the susceptibility artifact which is dark, an aqueous gadolinium solution marker shows up bright.

Another mechanism is possible if the medical device contains nuclei other than protons. In this case, it is possible to track the device due to the distinctive signal of this other nuclei, especially its frequency. Protons, hydrogen nuclei, have the advantage that they are abundant and have very good MRI sensitivity. They also have only two allowed spin states (nuclear spin=½). Nuclei with a spin greater than ½ have a quadrapole dipole moment, which broadens their NMR resonance signal. Fluorine-19 has reasonable sensitivity compared to ^1H and a resonant frequency that can be accommodated by the RF equipment in current scanners. Fluorine-19 also has a spin quantum number of ½, like hydrogen nuclei, giving it a sharp NMR signal.

What has been needed, and heretofore unavailable, in the art of interventional magnetic resonance angiography are medical devices (such as guidewires, catheters and implantable prostheses, e.g., stents) which contain passive markers for visualization under MRI. Such medical devices should provide a visible indication of the device during iMR angiography, without reliance upon susceptibility artifacts and signal voids. The present invention satisfies these and other needs.

SUMMARY OF THE INVENTION

Briefly, and in general terms, the present invention is directed to the design and configuration of medical devices for use in interventional magnetic resonance (iMR) angiography. The medical devices of the present invention incorporate compounds that contain fluorine-19 (^{19}F) nuclei for use as contrast agents and passive markers. MRI guided balloon angioplasty has been performed to demonstrate feasibility. Similarly, stent placement in humans under MRI has also been demonstrated. Configuration of such medical devices with ^{19}F markers will enhance the viability of iMR angiography. Since the art of MR angiography has relied on the use of gadolinium contrast agents and signal voids as passive markers, the use of contrast agents and markers containing fluorine-19 material provides a new and useful way for MRI.

A fluorine-19 containing marker may be used on any medical device which may benefit from enhanced MRI visibility. The fluorine marker of the device may encompass the device partially or wholly, meaning that the entire device may be partially, or wholly, constructed of a fluorine containing material. In addition, there may be more than one marker on the device. The device may be a guidewire, guiding catheter, angioplasty catheter, stent, embolic protection device, endovascular graft, endotracheal tube, Foley catheter, Hickman catheter, Broviac catheter, cerebrospinal fluid shunt, biliary stent, stylet, biopsy needle, electrode, percutaneous or endoluminal transducer or other desired interventional medical device. It may be a temporary or permanently implanted device. There are no limitations on the size, diameter, length or other materials of the device other than they must be MRI safe. The fluorine-19 material may be configured from an elastomer, a fluid, a fluorosilicone, or a perfluorocarbon grease or oil. It is advantageous that the fluorine-19 be incorporated in a physical form that is in a fluid, mobile state at the molecular level. This gives the fluorine-19 a sharp nuclear magnetic resonance signal. Such materials may be incorporated into marker bands and/or stripes, or may be deposited into or dispersed within the walls or lumens of the medical device to be visualized under interventional magnetic resonance angiography.

In one embodiment, a medical device including the present invention may be in the form of a balloon catheter assembly having a catheter tube having wall, an outer surface, a proximal end portion and a distal end portion. The device may further include an expandable member (balloon) associated with the distal end portion of the catheter and one more markers formed from fluorine-19 containing material. The markers may be in the form of a band or stripe formed within or disposed on the wall of the catheter. Similarly, a stent incorporating fluorine-19 containing material may be disposed on the balloon. In addition, fluorine-19 markers may be incorporated into endovascular grafts and embolic protection devices.

The use of fluorine-19 containing markers and contrast agents provides a novel method of performing angioplasty using magnetic resonance imaging. Such a method includes providing a catheter assembly including a catheter tube having an expandable member (balloon) formed on the distal end portion of the catheter and at least one marker having fluorine-19 containing material formed on the catheter tube and positioned proximate the expandable member. The distal end of the catheter is advanced to a desired location in a patient vasculature having a stenosis or other lesion. The vasculature, stenosis and the fluorine-19 containing material are visualized through magnetic resonance angiography. The balloon is inflated so as to expand the stenosis and open the vasculature, then the expandable member is contracted and the catheter and the expandable member are withdrawn from the patient vasculature. A stent mounted on a balloon catheter may be deployed in a similar manner.

Other features and advantages of the invention will become apparent from the following detailed description, taken in conjunction with the accompanying drawings, which illustrate, by way of example, the features of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts a partial perspective view of an embodiment of a catheter tube including an internal marker stripe of the present the invention.

FIG. 2 depicts a cross-sectional view along lines 2—2 of FIG. 1.

FIG. 3 depicts a partial perspective view of an embodiment of a catheter tube including a plurality of marker bands of the present the invention.

FIG. 4 depicts a cross-sectional view along lines 4—4 of FIG. 3.

FIG. 5 depicts a partial perspective view of an embodiment of a catheter tube including an external marker stripe of the present the invention.

FIG. 6 depicts a cross-sectional view along lines 6—6 of FIG. 5.

FIG. 7 depicts a transverse cross-sectional view of a catheter tube having an internal marker band.

FIG. 8 depicts a transverse cross-sectional view of a catheter tube having an external marker band.

FIG. 9 depicts a longitudinal cross-sectional view of a catheter tube having a plurality of lumens containing passive marker material.

FIG. 10 depicts a longitudinal cross-sectional view of a catheter tube having passive marker material dispersed within the wall of the catheter.

FIG. 11 depicts a longitudinal plan view in partial cross-section of an over-the-wire intravascular catheter assembly including marker bands of the present the invention.

FIG. 12 depicts a longitudinal plan view in partial cross-section of a rapid exchange intravascular catheter assembly including marker bands of the present the invention.

FIG. 13 depicts a perspective view of an embodiment of a stent including a plurality of marker bands of the present the invention.

FIG. 14 depicts a cross-sectional view along lines 14—14 of FIG. 13.

FIG. 15 depicts an alternate view of FIG. 14, including an external layer over the marker band.

FIG. 16 depicts a longitudinal plan view of an embodiment of an expanded embolic protection device, including a plurality of marker bands of the present the invention.

FIG. 17 depicts a longitudinal plan view of FIG. 16, wherein the embolic protection device is collapsed for delivery into a corporal lumen.

FIG. 18 depicts a perspective view of a graft assembly, including a plurality of marker bands of the present invention.

FIG. 19 depicts a longitudinal plan view of a stent delivery catheter assembly, including marker bands of the present invention.

FIG. 20 depicts a longitudinal plan view of a stent delivery catheter assembly, including marker bands of the present invention, which has been positioned proximate a lesion within a cross-section of a patient's vessel.

FIG. 21 depicts a longitudinal plan view of a stent delivery catheter assembly, including marker bands of the present invention, which has been positioned proximate a lesion within a cross-section of a patient's vessel, wherein the balloon and stent are fully expanded.

FIG. 22 depicts a longitudinal plan view depicting a partially withdrawn stent delivery catheter assembly, including marker bands of the present invention, wherein a stent has been deployed within a cross-section of a patient's vessel.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

As shown in the drawings for purposes of illustration, the present invention is directed to the design and configuration of medical devices for use in interventional magnetic resonance angiography. The medical devices of the present invention incorporate compounds which contain fluorine-19 (^{19}F) nuclei for use as contrast agents and passive markers. Interventional magnetic resonance (iMR) angiography is an active area of research. For example, MRI guided balloon angioplasty has been performed to demonstrate feasibility. Similarly, stent placement in humans under MRI has also been demonstrated. Configuration of such medical devices with ^{19}F markers will enhance the viability of iMR angiography.

To date, feasibility demonstrations of iMR angiography have relied on the use of gadolinium contrast agents or the signal void produced by magnetic susceptibility artifacts for the visualization of medical devices. Indeed, signal voids can make detection of a medical device possible. However, although a larger signal void enhances device detectability, the larger signal void compromises positional accuracy, as the signal void can be larger than the device. Since the signal from fluorine-19 will be distinct from a proton signal due to its frequency, it is believed that the use of contrast agents and markers containing fluorine-19 materials is a novel, useful improvement over the prior art.

Naturally occurring fluorine atoms (^{19}F) give a clear nuclear magnetic resonance signal, and thus can function as contrast agents or passive markers in MRI. The specific advantages for the use of ^{19}F include: 1) an extremely low native concentration in the body (fluorine is not naturally found in the body), 2) a high nuclear magnetic resonance sensitivity, 3) a magnetogyric ratio close to that of ^{1}H, thus permitting ^{19}F magnetic resonance imaging to be carried out with only minor modifications of existing MRI equipment, and 4) availability of biocompatible organofluorine-containing compounds.

Since ^{19}F is present in the body in very low concentration, a fluorine source must be administered to a subject to obtain a measurable ^{19}F magnetic resonance signal. Signal sensitivity is improved by administering higher concentrations of fluorine or by coupling the fluorine to a suitable probe or contrast agent that will concentrate in the body tissues of interest. High concentrations of fluorine containing compounds must be balanced against biocompatibility and increased tissue toxicity. It is also currently believed that a fluorine agent should preferably contain magnetically equivalent fluorine atoms in order to obtain a sharp, strong signal.

A ^{19}F containing marker may be used on any medical device which may benefit from enhanced MRI visibility. In addition, the fluorine marker may not be just a marker at all, meaning that the entire device may be partially, or wholly, constructed of a fluorine containing material. The device may be a guidewire, guiding catheter, angioplasty catheter, stent, embolic protection device, endovascular graft, endot-

racheal tube, Foley catheter, Hickman catheter, Broviac catheter, cerebrospinal fluid shunt, biliary stent, stylet, biopsy needle, electrode, percutaneous or endoluminal transducer or other desired interventional medical device. It may be a temporary or permanently implanted device. There are no limitations on the size, diameter, length or other materials of the device other than they must be MRI safe.

Since the use of medical devices under MRI guidance is an area of current research, it is not known with certainty whether active tracking or passive tracking strategies will prevail. An ^{19}F containing marker or device is a type of passive tracking. The significance of the invention is that it provides for a passive tracking mechanism to visualize devices under MRI. This scheme using fluorine nuclei involves no wires, circuits, connections, or moving parts. Since ^{19}F has a high sensitivity, the signal has the potential to be just as strong as the signal from water in adjacent tissues. However, since it will be at a different frequency, this signal can be displayed as a different intensity, or even a different color, to the physician. The materials required are available and biocompatible. Unlike passive markers, which use magnetic susceptibility, this approach does not produce a signal void. A large signal void may be quite visible, but the visibility comes at the expense of accurately positioning the device and visualizing anatomy in close proximity of the device. Susceptibility signal voids can extend beyond the dimensions of the device, and can change in dimension depending on the orientation of the device to the magnetic field.

One question is whether a separate scan will need to be performed to image the fluorine, or if the fluorine spins can be flipped concurrently with the proton spins and the resulting signals also received concurrently. Fortunately, fluorine-19 is the only isotope of fluorine naturally present. It is also not normally present in the body. However, simply using a conventional polymer that contains ^{19}F is not an optimum approach. To be useful, the fluorine must be in a form with a narrow range of chemical shifts. Consequently, the atoms must reside in elastomers, fluids or other rapidly rotating molecules, such as oils and greases. Fourier transform imaging techniques where a broad frequency excitation pulse is used to flip the spins could, potentially, be used to simultaneously image hydrogen and fluorine nuclei. One concern with this scheme is possibly confounding the frequency encoding scheme used to spatially locate the protons. The fluorine will resonant at a different frequency, raising the possibility that it might be confused with protons located in another part of the magnetic field gradient.

We can examine this possibility using performance specifications from a current, high performance 1.5 Tesla (T) scanner. For example, the Seimens Sonata MRI scanner has a forty centimeter field of view (FOV) and a maximum magnetic field gradient strength of forty mT/meter. At 1.5T, protons at what we will label the proximal end of the FOV will resonate at 63.86 MHz. If the maximum gradient is applied in the negative sense from this point, then at the distal end of the FOV, forty centimeters away, the proton resonant frequency will be 63.18 MHz. This frequency is still above the resonant frequency of the ^{19}F nuclei at the proximal end of the FOV, which will have a resonance frequency of 60.08 MHz. The scanner could be programmed to interpret any signal below a certain threshold to be from ^{19}F nuclei, and to apply different parameters for reconstructing their corresponding positions. Otherwise, a scan at the ^{19}F frequency may need to be interleaved with the normal proton pulse sequences. This would have the drawback of lengthening the overall RF pulse train with the potential of an overall longer scanning time and possibly lower temporal resolution. However, MRI software and hardware are rapidly improving in speed.

The majority of the signal in MRI comes from water. Tissues vary in their water content but for angiography, blood is the relevant tissue. Blood is approximately 93% water. This translates into a proton concentration of 103 moles/liter. Fluorine-19 has roughly 83% the sensitivity of hydrogen, hence a fluorine-19 concentration of 125 moles/liter will give a signal as strong as that of blood. However, MRI can image tissues with a lower water content. For example, grey matter and bone are 71% and 12% water respectively. A fluorine-19 concentration for equivalent sensitivity to these tissues is 95 and 16 moles/liter, respectively. Typical organofluorine compounds have fluorine-19 concentrations in this range. For example, perfluorooctane liquid has a fluorine-19 concentration of approximately 73 moles/liter. The perfluoroelastomer VITON (available from DuPont) has a fluorine-19 concentration in the range of 56–76 moles/liter (depending on grade). The common fluorosilicone (polymethyl-3,3,3-trifluoro-propylsiloxane) is approximately 27 moles/liter in fluorine-19. A suitable range of fluorine-19 concentration in a marker would be **15-75** moles/liter. This also applies to configurations in which the fluorine-19 is distributed throughout the entire device. It must be noted that MRI can image proton concentrations much lower than those of blood or grey matter. Image intensity is determined by the signal to noise (S/N) ratio. Faster acquisition of data or longer acquisition times both increase the signal to noise ratio. Also, it is not a matter of visualizing the fluorine-19 marker against a tissue background generated from a proton signal. This raises the issue of the contrast between the marker, or medical device, and tissue. The fluorine-19 generates a signal at a different frequency, which is detected by the imager and can be displayed with a different intensity, color, or even separately from the tissue image.

As the fluorine-19 marker, or fluorine-19 device is imaged, the marker or device will be represented as its true shape. A useful size for a marker is determined by the visibility required and constrained by the size of the medical device itself. In MRI, the imaging volume is broken down into elements called voxels. The device or marker can be physically smaller than a voxel as it is the RF signal given off by the marker that is detected.

When imaging devices in-vitro, a MRI phantom containing suitable hydrogen atoms is typically used. Phantoms of water, blood, yogurt, mineral oil, vegetable oil, and VASELINE (petroleum jelly) can be found in the literature. Petroleum jelly works since its protons are in adequately rapid motion. Similarly, a perfluorocarbon grease, or partially fluorinated grease or oil can serve as a marker. Such materials are soft and may need to be encapsulated into the device. A fully contained lumen or a dispersion of the grease into the body of the device would be adequate.

Perfluorocarbon oils and fluids are readily available. A common example is the vacuum pump oil FOMBLIN (available from Ausimont), which is used in pumps that are subject to very corrosive service. Other useful fluorine containing greases and fluids include, but are not limited to: FLUORONOZ (available from TECCEM), TRIFLUNOX (available from TECCEM), GALDEN (available from Ausimont), perfluoropolyether grease, trifluoropropylsilicone fluids, fluorosilicone fluids, perfluoropolyether fluids, perfluoroalkylether fluids, perfluoroalkanes, perfluoropropane, perfluorobutane, perfluoropentane, perfluorohexane, perfluoroheptane, perfluorooctane,

perfluorononane, perfluorodecane, perfluorocarbon emulsions, perfluoroalkylpolyester oils, perfluoropolyether solvent, fluorine containing freons, chlorofluorocarbons, and hydrochlorofluorocarbons.

Alternatively, bands of a fluorine containing elastomer can be affixed to a medical device for use in iMR angiography. Similarly, the elastomer could be coextruded as part of the device in the form of a strip or layer. Fluorine containing elastomers with a low glass transition temperature are available. For example, fluorosilicone is a commercially available elastomer with trifluoropropyl groups instead of methyl groups on the polymer backbone. With a glass transition temperature of less than −80° C., the fluorosilicone polymer chains are in rapid rotational motion at body temperature. Other useful fluorine containing elastomers include, but are not limited to: CHEMRAZ (available from Greene Tweed), VITON (available from DuPont), KEL-F (available from 3M), KALREZ (available from DuPont), FLUOREL (available from 3M), copolymers of vinylidene fluoride and hexafluoropropene, copolymers of chlorotrifluorethylene and vinylidene fluoride, poly (trifluoropropylmethylsiloxane), fluorosilicone elastomers, polymethyl-3,3,3-trifluoro-propylsiloxane, polymethyl-3,3, 3-trifluoropropyl-dimethylsiloxane copolymer, and perfluororesins.

Further, a fluorine containing inflation medium may be used to visualize a balloon catheter during iMR angiography. Inflation fluids are used to inflate balloon angioplasty catheters (e.g., PTCA catheters). This is currently accomplished under x-ray fluoroscopy with a radiopaque contrast agent to render the balloon more visible. A fluorine containing fluid (contrast agent) could also be used to inflate the catheter. This would render the balloon catheter visible when imaged via ^{19}F MR imaging. Such fluids need to be very safe, as it is possible for balloons to rupture or pinhole during inflation and use. An obvious choice would be the perfluoro emulsions used as synthetic blood. One example is Oxycyte produced by Synthetic Blood International. Perfluorocarbons with a sufficiently low vapor pressure such as perfluorodecalin and perfluorotetramethylcyclohaxane are suitable for making emulsion blood substitutes. Alternatively, the marker may be formed within the material of the balloon (expandable member), or the balloon material itself may contain fluorine-19 containing compounds.

The drawings show various embodiments of the present invention. Referring now to FIG. **1**, an embodiment of a catheter tube **30** incorporating the present invention is shown. The catheter tube generally includes an outer surface **32** and a wall **34** forming an inner lumen **36**. The catheter tube may be formed by conventional means and from conventional method and materials, such as polyesters, polyurethanes and other MRI safe materials. Since such materials generally create a signal void under MR angiography, a marker **40** is included in the catheter tube wall. As shown in FIGS. **1** and **2**, the marker **40** includes a stripe **42** extending along the outer surface and parallel to the longitudinal axis of the catheter. In this first embodiment, the marker stripe is located proximate the outer surface of the catheter tube. The stripe may extend the full length of the catheter tube or may only extend along certain portions which require visualization during an interventional procedure.

Referring now to FIGS. **3** and **4**, a catheter tube **50** of the present invention having an outer surface **52**, a wall **54** and a lumen **56** is shown. In this alternative embodiment, a plurality of marker bands **62**, **60** are shown extending circumferentially around the catheter tube. The marker bands may be embedded within the catheter wall, or may be placed on the outside surface of the wall. These marker bands may be made of any fluorine-19 containing compound as described herein.

Referring now to FIGS. **5** and **6**, a catheter tube **70** having a surface **72**, a wall **74** and a lumen **76** is shown. This embodiment of the present invention includes a marker stripe **78** located on the outer surface of the catheter tube. The marker stripe may be constructed from any suitable ^{19}F elastomer as described herein. The marker stripe may be affixed to the catheter tube via gluing, bonding or other similar means.

Referring now to FIG. **7**, a cross-section of a catheter tube is shown, wherein a marker band **84** is embedded within a wall **80** of the catheter, but not within a catheter lumen **82**. As shown in FIG. **8**, a marker band **94** is disposed on the outside of a catheter wall **90** having a catheter lumen **92**. Alternatively, the marker band or stripe may be included within the catheter lumen.

Referring now to FIG. **9**, a catheter tube **100** or similar device is shown having a wall **102** and lumen **104**. Cylindrical pockets or lumens **106**, **108** of perfluorogrease, or other fluorine-19 containing material, may be formed in the wall of the catheter, so as to provide one or more marker bands for MR angiography. Alternatively, the pockets of perfluorogrease can extend the longitudinal length of the catheter, thereby creating a marker stripe. Alternatively, as shown in FIG. **10**, a catheter tubing **110** or similar device may contain multiple pockets or fluid droplets **116** of a perfluorogrease or fluorine-19 emulsion within its wall **112** and outside of its lumen **114**. Since such greases and emulsions are soft, the ^{19}F containing materials should be encapsulated in or dispersed into the wall of the catheter or similar device.

Referring now to FIG. **11**, the fluorine-19 markers of the present invention may be incorporated into an over-the-wire (OTW) catheter assembly **120**, having proximal portion **121** and distal portion **122**. The proximal portion of the catheter assembly may include an inflation port or side arm **124** and catheter tube **126**. The distal portion of the catheter assembly may include the catheter tube and a balloon (expandable member) **128** mounted on or secured to the distal end of the catheter tube. The distal portion of the catheter tube is formed with a lumen **132** in which an elongate inner tubular member **130** is disposed. A guidewire **138** may be slidably positioned within the inner tubular member. To enable the visualization of the catheter under MR angiography, one or more marker bands **134**, **135** and **136** are provided in the OTW catheter assembly. As by way of example, a marker band **134** is disposed on or within the catheter tube just proximal the balloon. Similarly, a second marker band **136** may be disposed on or imbedded within the distal end of the balloon. Further, a marker band **135** may be disposed on or within the inner tubular member so as to indicate the relative center or other portion of the balloon. Alternatively, as discussed above, the catheter tube may contain an elastomeric stripe, or lumens including perfluorogrease or similar fluorine-19 containing emulsion. In addition, the guidewire **138** may contain or be constructed of a fluorine-19 containing material. Similarly, distal end **139** of the guidewire may be made from a perfluorocarbon elastomer or contain a lumen having perfluorogrease or emulsion.

Referring now to FIG. **12**, fluorine-19 containing marker bands or similar devices may be included in a rapid exchange (Rx) catheter assembly. The catheter assembly **140** includes a proximal end **141** and a distal portion **142**. The

proximal end of the catheter may include an inflation port **144**. A distal portion of the Rx catheter includes a catheter tube **146**, balloon (expandable member) **148** and an elongate inner tubular member **150** included within the lumen **152** of the balloon and tubular member. In accordance with the present invention, the Rx catheter assembly may include one or more marker bands **154**, **155** and **156**. A first marker band **154** may be disposed on or within the catheter tube just proximal of the balloon. In addition, a second marker band **156** may be included just distal the balloon and along the portion of the catheter tube that joins to the inner tubular member. In addition, a third marker band **155** may be included on or within the inner tubular member and proximate the center of the balloon. As discussed above, the catheter assembly may alternatively include an fluorine-19 containing elastomer stripe, or lumens including a perfluorogrease or emulsion. Further, a guidewire **158** may disposed within the inner tubular member and may contain or be constructed of a fluorine-19 containing material. The distal end **159** of the guidewire may include marker bands, be constructed of an elastomer or other fluorine-19 containing material, or may be embedded with a perfluorogrease or emulsion, as discussed above.

Referring now to FIG. **13**, and by way of example, the present invention may be incorporated into a stent or similar endoprosthesis **160**. Such a stent may be balloon expandable or self-expanding. Such stents may be made of any suitable biocompatible material, such as AISI 316L stainless steel, nitinol (nickle-titanium alloys) or polymers. Such a stent may be of a ring and link pattern as shown in FIG. **13**, or other configurations, such as, but not limited to a zigzag design, a coil design or tubular mesh design, as known in the art or to be determined in the future. By way of example, the stent may include a plurality of marker bands or rings **162**, **163** and **164**, which include a fluorine-19 compound either included within the structure of the stent or secured to the outside as heretofore described. In addition one or more of the links **166** may contain or be coated with a fluorine-19 containing material.

Referring to FIGS. **14** and **15**, the stent **160** may include a fluorine-19 containing material **168** coated, bonded or other wise disposed on the outside of the base material **167** (for example, stainless steel, nitinol or polymer). Conversely, fluorine-19 containing material may be embedded between the base layer **167** and a outer layer **169** of the stent. The outer layer of the stent may be the same material as the base layer, or may be of another material such as a more biocompatible metal, polymer or a drug delivery component.

Referring now to FIGS. **16** and **17**, and by way of example, the present invention may be incorporated into an embolic protection device **170**. Such device may include a filter assembly **172** and expandable strut assembly **174**. The embolic protection device may further include an elongate tubular member **180**, within which may be disposed a guidewire **182** for positioning the device within a corporeal lumen. In accordance with the present invention, the embolic protection device may include a plurality of marker bands **186**, **187** and **188**, which include fluorine-19 containing material. These marker bands may be incorporated into the embolic protection device as heretofore described. In addition, the filter assembly may be constructed from a material such as a perfluorocarbon elastomer, or may contain a dispersion of perfluorogrease or emulsion as heretofore described. Similarly, the expandable strut assembly may include struts **176**, **178**, which may also contain fluorine-19 containing material or may be constructed from the same. In addition, the guidewire may include or be constructed from a fluorine-19 containing material and the distal end of the guidewire **184** may also include or be constructed from a fluorine-19 containing material.

Referring now to FIG. **18**, the fluorine-19 marker system of the present invention may be incorporated into a bifurcated graft **200**. Likewise, the marker system may be incorporated into a tubular graft (not shown). Such a graft includes a Dacron, Teflon or other suitable flexible material having an upper body **202**, a first leg **203** and a second leg **204**, wherein the legs are joined to the upper body. Such a configuration forms a "Y" or "pants leg" configuration. A plurality of closely spaced markers **206** formed from a compound containing a fluorine-19 may be configured on the outside of the first and second legs. Similarly, wider spaced markers **208** may be configured on the inside of the legs of the bifurcated graft (or visa versa). Such markers may be formed from an elastomer or similar fluorine-19 containing material as heretofore described, which may be sewn, glued or otherwise bonded to the graft. In addition, the graft material forming the body and the bifurcated legs may be made of a fluorine **19**-containing material or may incorporate such a material. In many such grafts, such as those used for repairing abdominal aortic aneurysms, the upper body may include a first attachment system **210** proximate an upper opening of the graft. Tube grafts may contain a like attachment system at the lower opening of the graft. Similarly, bifurcated grafts may include smaller attachment systems **212** positioned at the end of the legs and proximate the lower openings of the graft. As heretofore described regarding stents (FIGS. **13–15**), the attachment system may be made of a variety of materials and may incorporate a fluorine-19 marker system. Such stents and attachment systems may be of various configurations, such as, but not limited to, a ring and link design, a zigzag design, a coil design or tubular mesh design. Also as heretofore described, the attachment systems, like stents, may be coated with or otherwise contain a fluorine-19 marker material and may be further coated with a biocompatible or other desired material.

When combined with a delivery catheter assembly, the fluorine-19 markers of the present invention result in an improved process and method for delivering and implanting a stent or other endoprosthesis to a desired location within a patient's vasculature using interventional magnetic resonance angiography. FIGS. **19** through **22** illustrate, by way of example, a method of delivering and implanting a stent **160** mounted on a balloon **148** of a catheter tube **146**, including fluorine-19 containing marker bands **154**, **156**, **162**, **163** and **164**. While the drawing figures illustrate a rapid exchange (Rx) intravascular catheter **140** and guidewire **158**, embodiments of the fluorine-19 markers of the present invention may be also used with an over-the-wire (OTW) intravascular catheter. Additionally, although the marker system is shown in combination with a balloon expandable stent and associate catheter assembly, the marker system may be used with a self-expanding stent in combination with an appropriate alternative catbeter assembly. Likewise, the system may bc used in an angioplasty (e.g., PTCA) procedure, without implanting a stent.

The figures illustrate a situation in which the stent delivery catheter having a fluorine-19 marker system is used after an intravascular procedure has created a dissection in the arterial lining to such an extent that the lining needs support to prevent the dissection from collapsing into the arterial passageway and impeding sufficient blood flow through the vessel. In addition, the stent delivery catheter having a

fluorine-19 marker system may be used in a balloon angioplasty procedure in which a stent is used to support the vasculature to prevent restenosis. Furthermore, the procedures and devices described herein may be adapted by one of ordinary skill in the art to any procedure where endoprosthesis is to be placed into a body lumen.

As shown in FIG. **19**, a catheter assembly **140** is provided with a balloon expandable stent **160** removably secured on an expandable member (balloon) **148** formed on or secured to catheter tube **146**. Marker bands **154** and **156** are included on the catheter tube. Alternatively, marker systems as described in FIGS. **1** to **17** may also be used. Further, fluorine-19 markers **162**, **163** and **164** are attached to or imbedded within the stent as heretofore described. In addition, a guidewire **158**, which may include a marker system, is disposed within the catheter assembly.

Referring to FIG. **20**, the catheter assembly is inserted into the lumen of a vessel **190** of a patient's vasculature, such as a coronary artery, and over the guidewire **158** having a distal end **159**, which is previously positioned distal to the desired location **194** requiring support. The distal portion of the catheter assembly, including the balloon and stent, is then moved in a distal direction until the balloon and stent are positioned proximate a lesion **192** or stenosis at the desired location of the patient's vasculature.

As illustrated in FIG. **21**, once the stent **160** is positioned at the desired location **194** of the vessel **190**, the balloon **148** of the catheter tube **146** is inflated. This may be accomplished, for example, by injecting inflation fluid under substantial pressure into a lumen of the catheter tube. For added contrast, under iMR angiography, the inflation fluid may include a fluorine-19 containing compound, such as described herein. As the balloon expands, the stent also expands, until it is fully expanded and implanted in the vessel. After the stent is fully expanded, the balloon is then deflated or otherwise contracted; however, the expandable stent remains implanted at the desired location in the vessel. Once the stent is no longer in contact with the catheter assembly, then the catheter, balloon and guidewire **158** are withdrawn from the vasculature (FIG. **22**).

The dimensions of the intravascular catheter will generally follow the dimensions of intravascular catheters used in angioplasty procedures in the same arterial location. Typically, the length of a catheter assembly for use in the coronary arteries is about one hundred and fifty centimeters, the outer diameter of the catheter expandable member is about 0.89 millimeters, the length of the balloon is typically about two centimeters and the inflated diameter of the balloon is about one to about eight millimeters, depending upon the application. Catheter dimensions for peripheral use will vary, and is known in the art. The materials of construction of the catheter assembly, catheter tube and expandable member may be selected, for example, from those used in conventional balloon angioplasty catheters. Furthermore, the specific dimensions and materials of construction of the detachable sheath are provided as examples, and substitutes are readily contemplated which do not depart from the invention.

While the present invention has been described herein in terms of delivering an expandable stent to a desired location within a patient's blood vessel, the delivery catheter can also be employed to deliver stents to locations within other body lumens so that the stents can be expanded to maintain the patency of those body lumens. In addition, the detachable sheath may be used to removably secure self-expanding stents to delivery catheters.

While particular forms of the invention have been illustrated and described, it will also be apparent to those skilled in the art that various modifications can be made without departing from the spirit and scope of the invention. More specifically, it should be clear that the present invention is not limited to catheters, tubular type stents or embolic protection devices. Likewise, the invention is not limited to any particular method of forming the underlying medical device structure. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

What is claimed is:

1. A medical device for use in a interventional magnetic resonance angiography, comprising a compound containing fluorine-19.

2. The medical device of claim **1**, wherein the compound containing fluorine-19 is an elastomer.

3. The medical device of claim **1**, wherein the compound containing fluorine-19 is a fluid.

4. The medical device of claim **1**, wherein the compound containing fluorine-19 is a fluorosilicone.

5. The medical device of claim **1**, wherein the compound containing fluorine-19 is a perfluorocarbon grease.

6. The medical device of claim **1**, wherein the compound containing fluorine-19 is an elastomer selected from the group consisting of CHEMRAZ, VITON, KEL-F, KALREZ, FLUOREL, copolymers of vinylidene fluoride and hexafluoropropene, copolymers of chlorotrifluoroethylene and vinylidene fluoride, poly (trifluoropropylmethylsiloxane), fluorosilicone elastomers, polymethyl-3,3,3-trifluoro-propylsiloxane, polymethyl-3,3,3-trifluoropropyl-dimethylsiloxane copolymer and perfluoresins.

7. The medical device of claim **1**, wherein the compound containing fluorine-19 is a fluid selected from the group consisting of FLUORONOZ, TRIFLUNOX, FOMBLFN, GALDEN, perfluoropolyether grease, trifluoropropylsilicone fluids, fluorosilicone fluids, perfluoropolyether fluids, perfluoroalkylether fluids, perfluoroalkanes, perfluoropropane, perfluorobutane, perfluoropentane, perfluorohexane, perfluoroheptane, perfluorooctane, perfluorononane, perfluorodecane, perfluorocarbon emulsions, perfluoroalkylpolyester oils, perfluoropolyether solvent, fluorine containing freons, chlorofluorocarbons and hydrochlorofluorocarbons.

8. A medical device, comprising means for visualizing under magnetic resonance angiography, wherein the means for visualizing includes a compound containing fluorine-19.

9. The medical device of claim **8**, wherein the compound containing fluorine-19 is an elastomer having a fluorine-19 concentration in the range of 15 to 125 moles/liter.

10. The medical device of claim **8**, wherein the compound containing fluorine-19 is a fluid having a fluorine-19 concentration in the range of 15 to 125 moles/liter.

11. The medical device of claim **8**, wherein the means for visualizing forms a marker band.

12. The medical device of claim **8**, wherein the means for visualizing forms a marker stripe.

13. The medical device of claim **8**, wherein the means for visualizing is dispersed within the medical device.

14. A catheter assembly, comprising:

a catheter tube having wall, an outer surface, a proximal end portion and a distal end portion; and

a marker formed from fluorine-19 containing material.

15. The catheter assembly of claim **14**, wherein the marker is a stripe formed within the wall of the catheter tube.

16. The catheter assembly of claim **14**, wherein the marker is a stripe formed on the outer surface of the catheter tube.

17. The catheter assembly of claim **14**, wherein the marker is a band formed within the wall of the catheter tube.

18. The catheter assembly of claim **14**, wherein the marker is a band formed on the outer surface of the catheter tube.

19. The catheter assembly of claim 14, wherein the marker is dispersed within the wall of the catheter tube.

20. The catheter assembly of claim 14, further including an expandable member associated with the distal end portion of the catheter, wherein a marker containing fluorine-19 material is formed within the expandable member.

21. A balloon catheter assembly, comprising:

a catheter tube having wall, an outer surface, a proximal end portion and a distal end portion;

an expandable member associated with the distal end portion of the catheter;

a first marker having fluorine-19 containing material formed on the catheter tube and positioned proximal of the expandable member; and

a second marker having fluorine-19 containing material formed on the catheter tube and positioned distal of the expandable member.

22. The catheter assembly of claim 21, further including an elongate tubular member disposed within the expandable member and having a marker with fluorine-19 containing material.

23. An endoprosthesis for implanting in a body lumen, comprising a body having an outer surface, the body including a compound containing fluorine-19 positioned proximate the outer surface.

24. A stent, comprising a body having an outer surface, the body including a compound containing fluorine-19 positioned proximate the outer surface.

25. The stent of claim 24, further comprising plurality of struts including a compound containing fluorine-19.

26. An embolic protection device, comprising a filter having an outer surface, the filter including a compound containing fluorine-19 positioned proximate the outer surface.

27. The embolic protection device of claim 26, further comprising an elongate tubular member including a marker formed from a compound containing fluorine-19.

28. The embolic protection device of claim 27, further comprising plurality of struts including a compound containing fluorine-19.

29. A graft, comprising a body including a marker formed from a compound containing fluorine-19.

30. The graft of claim 29, further comprising:

a first leg in fluid communication with the body and having at least one marker formed from a compound containing fluorine-19; and

a second leg in fluid communication with the body and having at least one marker formed from a compound containing fluorine-19.

31. A method of performing angioplasty using magnetic resonance angiography, the method comprising:

providing a catheter assembly including,

a catheter tube having a proximal end portion and a distal end portion,

an expandable member formed on the distal end portion of the catheter tube,

at least one marker having fluorine-19 containing material formed on the catheter tube and positioned proximate the expandable member, and

advancing the distal end portion of the catheter and the expandable member to a desired location in a patient vasculature having a stenosis;

visualizing vasculature, stenosis and the fluorine-19 containing material through magnetic resonance angiography,

expanding the expandable member so as to expand the stenosis and open the vasculature;

contracting the expandable member; and

withdrawing the catheter and the expandable member from the patient vasculature.

32. The method of claim 31, further comprising using a fluorine-19 containing contrast agent when expanding the expandable member, and visualizing the contrast agent through magnetic resonance angiography.

33. A method of delivering a stent into a desired location within a patient's vasculature, the method comprising:

providing a catheter assembly including,

a catheter tube having a proximal end portion and a distal end portion,

a balloon formed on the distal end portion of the catheter tube, and

a stent disposed on the balloon and configured with a body having an outer surface, the body including fluorine-19 containing material positioned proximate the outer surface;

advancing the distal end portion of the catheter tube, the balloon and the stent though the vasculature to a desired location;

visualizing the fluorine-19 containing material through magnetic resonance angiography;

inflating the balloon so as to expand the stent into the desired location;

deflating the balloon; and

withdrawing the catheter tube and the balloon from the vasculature.

34. The method of claim 33, further comprising using a fluorine-19 containing contrast agent when inflating the balloon, and visualizing the contrast agent through magnetic resonance angiography.

35. The method of claim 33, further comprising providing a first marker having fluorine-19 containing material formed on the catheter tube and positioned proximal of the balloon, providing a second marker having fluorine-19 containing material formed on the catheter tube and positioned distal of the expandable member, and visualizing the fluorine-19 containing material formed on the catheter tube through magnetic resonance angiography.

36. A stent, comprising a body formed from a base material having an outer surface, the body further including a compound containing fluorine-19.

37. The stent of claim 36, wherein the compound containing fluorine-19 is an elastomer.

38. The stent of claim 37, wherein the elastomer is disposed on the outer surface of the base material.

39. The stent of claim 37, wherein the elastomer is disposed between the outer surface of the base material and an outer layer of the body.

40. The stent of claim 36, wherein the compound containing fluorine-19 is a fluorosilicone.

41. The stent of claim 40, wherein the fluorosilicone is disposed on the outer surface of the base material.

42. The stent of claim 40, wherein the fluorosilicone is disposed between the outer surface of the base material and an outer layer of the body.

43. The stent of claim 36, wherein the compound containing fluorine-19 is a fluid.

44. The stent of claim 43, wherein the fluid is dispersed within the base material.

45. The stent of claim 36, wherein the compound containing fluorine-19 is a perfluorocarbon grease.

46. The stent of claim 45, wherein the perfluorocarbon grease is dispersed within the base material.

* * * * *

Appendix E

US 20030144727A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0144727 A1**

Rosenthal et al. (43) **Pub. Date: Jul. 31, 2003**

(54) **MEDICAL DEVICE FOR DELIVERING BIOLOGICALLY ACTIVE MATERIAL**

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(21) Appl. No.: **10/062,794**

(22) Filed: **Jan. 31, 2002**

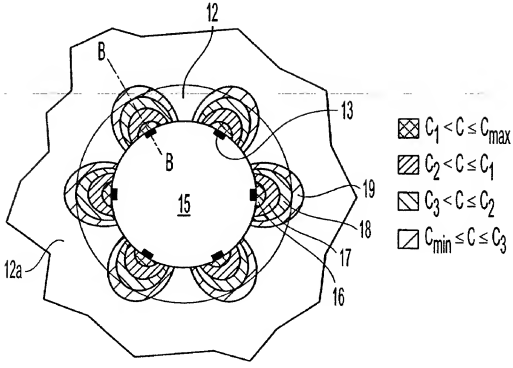
Publication Classification

(51) **Int. Cl.**[7] **A61F 2/06**

(52) **U.S. Cl.** **623/1.15**; 623/1.42

(57) **ABSTRACT**

A medical device for delivering a biologically active material into a body tissue, comprising struts and optionally the biologically active material. In an embodiment, the medical device comprises non-structural elements integral with the struts. A method for designing such medical device are also disclosed. Another embodiment is a medical device having an outer surface comprising a middle section and end sections. The end sections have a greater available surface area, greater affinity for or a greater amount of the biologically active material per unit length of the outer surface than the middle section. The middle section may be covered with a barrier layer. Another embodiment is a medical device comprising a rectangular portion having a greater capacity for carrying a biologically active material per unit length of the outer surface. A method for delivering a biologically active material to a body tissue is also disclosed.



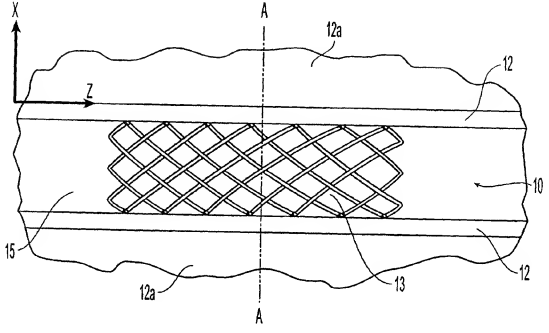
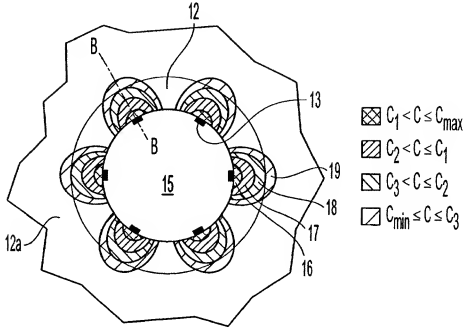


Fig. 1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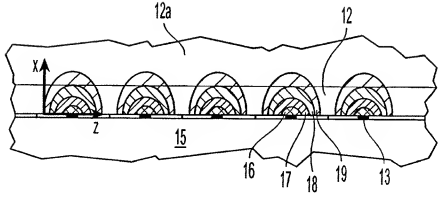
B
B
13
15
19
18
17
16
12a
$C_1 < C \leq C_{max}$
$C_2 < C \leq C_1$
$C_3 < C \leq C_2$
$C_{min} \leq C \leq C_3$

Fig. 2A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12
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19
13

Fig. 2B

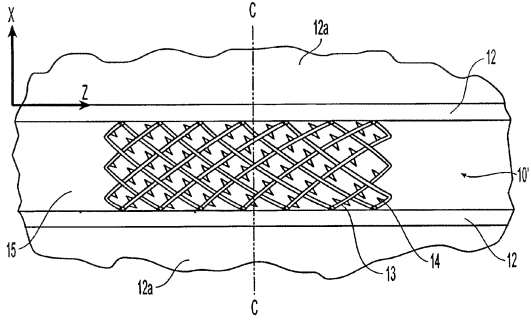
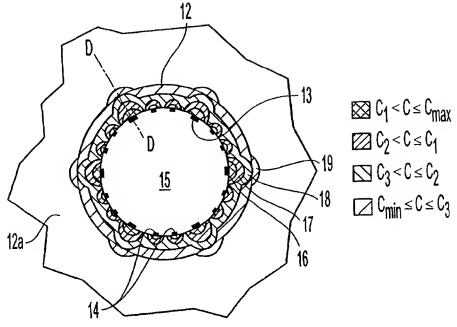


Fig. 3


12
D
D
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19
18
17
16
12a
14
$C_1 < C \leq C_{max}$
$C_2 < C \leq C_1$
$C_3 < C \leq C_2$
$C_{min} \leq C \leq C_3$

Fig. 4A

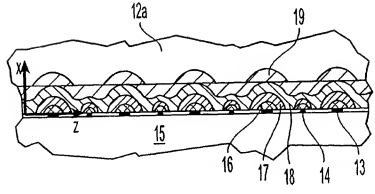
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Fig. 4B

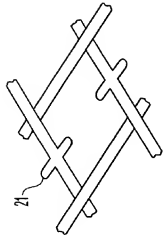

Fig. 6

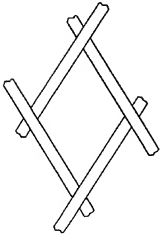

Fig. 5

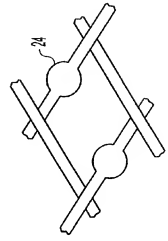

Fig. 9

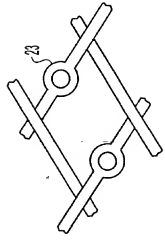

Fig. 8

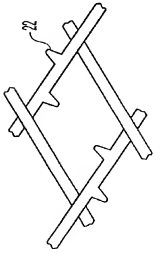

Fig. 7

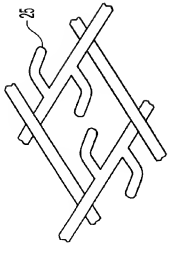

Fig. 10

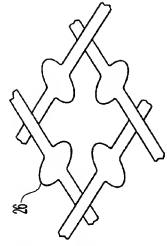

Fig. 11

Fig. 12

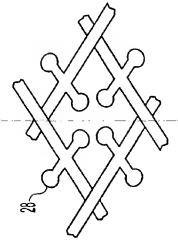

Fig. 13

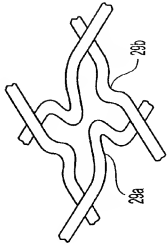

Fig. 14

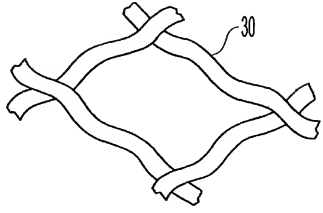

Fig. 15

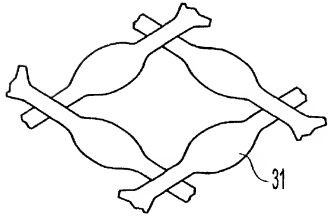

Fig. 16

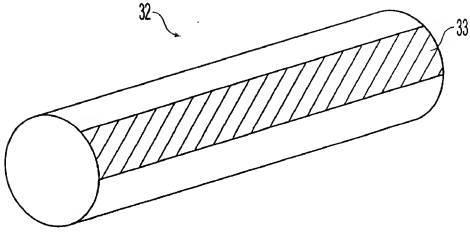

Fig. 17

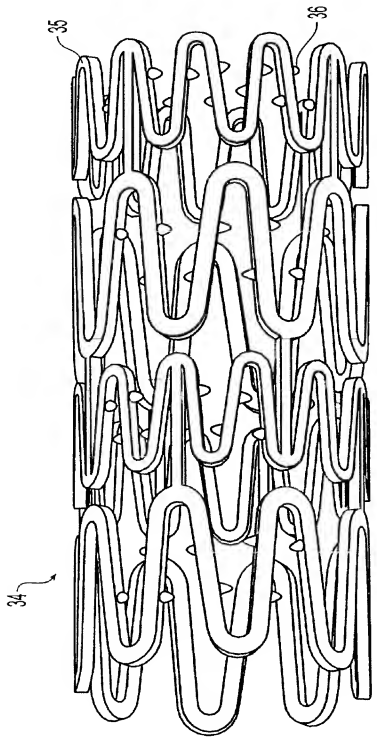

Fig. 18

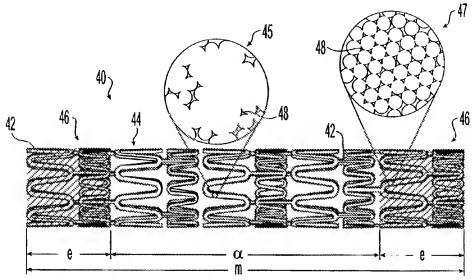

Fig. 19

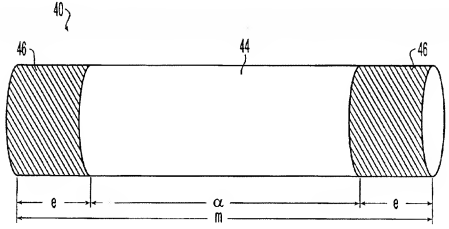

Fig. 20

MEDICAL DEVICE FOR DELIVERING BIOLOGICALLY ACTIVE MATERIAL

FIELD OF THE INVENTION

[0001] This invention relates generally to medical devices, such as stents, for delivering a biologically active material to a desired location within the body of a patient. More particularly, the invention is directed to a medical device comprising a plurality of struts and a plurality of non-structural elements integral with the struts, wherein the struts and the non-structural elements comprise the biologically active material. The invention is also directed to a method for delivering the biologically active material to body tissue of a patient by inserting this medical device into body of the patient, and further a method for designing such medical device.

[0002] The invention is also directed to a medical device comprising a plurality of struts and having an outer surface wherein the outer surface which has a middle section and end sections. The end sections of the outer surface either (1) contain a greater amount of a biologically active material per unit length of the outer surface or (2) have a greater capacity per unit length to contain such material than the middle section of the outer surface by having a greater surface area per unit length of the outer surface than the middle section or having a greater affinity for the biologically active material per unit length of the outer surface than the middle section.

BACKGROUND OF THE INVENTION

[0003] A variety of medical conditions have been treated by introducing an insertable medical device having a coating for release of a biologically active material. For example, various types of biologically active material-coated medical devices, such as stents, have been proposed for localized delivery of the biologically active material to a body lumen. See, e.g., U.S. Pat. No. 6,099,562 to Ding et al. However, it has been noted that, with existing coated medical devices, the release profile of a biologically active material may not be uniform along the entire length of the medical device.

[0004] For example, even if a biologically active material having a pharmacological effect is delivered to a body tissue, such effect may not result if the concentration of the biologically active material in the body tissue is below a certain concentration. Such concentration is referred to as the minimum effective concentration (C_{min}) of the biologically active material in the body tissue. Each biologically active material has different C_{min}. C_{min} of a biologically active material also varies depending on the type of body tissue to which it is delivered. On the other hand, a biologically active material becomes toxic if its concentration is higher than a certain concentration. Such concentration is referred to as the maximum effective concentration C_{max}. In addition, it is insufficient that the mean concentration of the biologically active material delivered through out the body tissue to be treated is greater than C_{min} and smaller than C_{max}. The concentration of the biologically active material at each and every area throughout the body tissue to be treated should be equal to or greater than C_{min} but equal to or smaller than C_{max} of the biologically active material. For instance, when a coated stent comprised of struts, such as the stent shown in **FIG. 1**, is used as a medical device for delivering a hydrophobic biologically active material, concentrations of the biologically active material may significantly differ between the regions of the tissue adjacent to the struts and the regions of the tissue farther from the struts. See Hwang et al., http://www.circulationaha.org (accepted in April 2001). Even if the mean concentration of the biologically active material in the tissue surrounding the stent is above C_{min} of the biologically activc material and at or under C_{max}, the concentrations at certain regions of the tissue to be treated, which are farther from the struts, may not reach C_{min}. Also, if the amount of the biologically active material in the coating is increased to achieve a concentration higher than C_{min} at all regions of the tissue to be treated, then the concentrations at regions of the tissue adjacent to the struts may exceed the toxic levels, as explained below using the figures.

[0005] In **FIG. 1**, the coated stent **10** is placed in a blood vessel **15** having a vessel wall **12** to be treated. This vessel wall is surrounded by tissue **12***a*. The biologically active material coated on struts **13** of the stent **10** is released into the vessel wall **12** to be treated. **FIG. 2** is a cross sectional view along line A of the stent **10** in **FIG. 1**. **FIG. 2** also shows the concentration levels of the biologically active material in each area surrounding the struts **13** at a certain time after the insertion of the stent into the vessel **15**. The area adjacent to the struts, i.e., the area between the struts **13** and line **16**, has a concentration level at or below C_{max}, which is just below the toxic level. The farther from the struts **13** the tissue to be treated is located, the lower the concentration of biologically active material delivered to the tissue becomes. However, the area between line **18** and line **19** has the concentration level at or higher than C_{min}. A concentration of the biologically active material in the area outside line **19** is below C_{min}.

[0006] Also, **FIGS. 2A and 2B** clearly show that there are gaps between each strut **13** wherein the vessel wall to be treated does not receive sufficient biologically active material to have C_{min}. The areas within line **19**, i.e., having concentrations above C_{min}, may be increased in size to include more area of the vessel wall to be treated **12**, if the amount of the biologically active material on the struts **13** is increased. However, by doing so, the concentration of the biologically active material in the area adjacent to the struts **13** may exceed the toxic level. Accordingly, there is a need for a medical device comprising a plurality of struts that can achieve the biologically active material concentrations that is above C_{min} and below toxic levels throughout the tissue.

[0007] Also, with existing coated medical devices, generally, the coating is uniformly applied along the entire length of the device or surface of the device. For example, conventional coated stents are coated uniformly along the entire length of the surface of the device. The biologically active material-concentration-profile along the length of the coated surface may be in the shape of a bell-curve, wherein the concentration of the biologically active material released at the middle of the surface is greater than the concentration of the biologically active material released at the ends of the coated surface. This uneven concentration-profile along the length of the coated surface may lead to the application of an inadequate or sub-optimal dosage of the biologically active material to the body tissue located at the ends of the coated surface. It is possible that such uneven local concentration of the biologically active material along the length of

the coated surface of the medical device may lead to undesired effects. For example, in the case of a biologically active material-coated stent used to prevent or treat restenosis, if the amount of biologically active material delivered to the tissue located at the ends of the stent is sub-optimal, it is possible that restenosis may occur in such tissue.

[0008] The biologically active material dosage at the tissue located at the ends of the coated surface of the medical device can be increased if the concentration or amount of the biologically active material is increased along the entire length of the surface. However, by increasing the concentration or amount of biologically active material released along the entire surface, the dosage delivered to tissue located at the middle of the surface may be too great or even at toxic levels. Thus, there is a need for a medical device that can realize a more uniform concentration-profile for biologically active material along the entire length of a coated surface of a medical device and avoid the possibility of undesired effects accompanied by an uneven biologically active material concentration-profile.

[0009] Moreover, medical devices wherein a biologically active material is uniformly coated on the entire outer surface of the medical devices that is exposed to body tissue are generally used to deliver such biologically active material to specific parts of such body tissue. For instance, such devices are used to treat lesions in body lumen. However, because the entire outer surface of the device contains the biologically active material, this biologically active material will be delivered to healthy body tissue in addition to the lesion. Treatment of healthy tissue with the biologically active material is not only unnecessary but maybe harmful. Accordingly, there is a need for a medical device that can realize an asymmetry release-profile of biologically active material to deliver such material to only a limited region of the body tissue that requires the biologically active material.

SUMMARY OF THE INVENTION

[0010] These and other objectives are accomplished by the present invention. To achieve the aforementioned objectives, we have invented a medical device for delivering a biologically active material into a body tissue of a patient; a method for designing such device; and a method for delivery of a biologically active material to a body tissue.

[0011] The medical device of the invention is a medical device for delivery of biologically active materials to a body tissue of a patient in need of treatment. The medical device comprises struts and non-structural elements integral with the struts, and those struts and non-structural elements comprise the biologically active material. In an embodiment, the medical device comprises a tubular portion having an outer surface, and the non-structural elements are distributed throughout the outer surface. In another embodiment, the non-structural elements are located in a radially asymmetric distribution on the outer surface. In yet another embodiment, the outer surface has end sections and a middle section, and the end sections comprise a greater number of the non-structural elements per unit length of the outer surface than the middle section.

[0012] The present invention is also directed to a method for delivering a biologically activc matcrial to body tissuc of a patient which comprises inserting the above-mentioned medical device into the body of the patient.

[0013] Further, the present invention is directed to a method for designing such medical device. The method comprises: providing a preliminary medical device comprising struts in a geometric pattern wherein the struts comprise the biologically active material; determining a concentration-profile for the biologically active material which is released from the preliminary medical device; and modifying the geometric pattern of the struts of the preliminary medical device by incorporating non-structural elements comprising the biologically active material that are integral with the struts to achieve more desired distribution of the biologically active material in the body tissue.

[0014] The present invention is also directed to a medical device insertable into the body of a patient. The medical device has an outer surface comprising struts, and the outer surface has a middle section and end sections. The end sections have a greater available surface area per unit length of the outer surface than the middle section. In another embodiment, the end sections have greater affinity for the biologically active material per unit length of the outer surface than the middle section. In yet another embodiment, the end sections have a greater amount of the biologically active material per unit length of the outer surface than the middle section. Further, in another embodiment, at least a part of each of the middle section and the end sections is covered with a coating comprising the biologically active material, and the middle section comprises a barrier layer placed over the coating covering the middle section.

[0015] Moreover, the present invention provides another embodiment of the medical device for treating body tissue. The medical device comprises an outer surface comprising struts. The outer surface has a rectangular portion having a greater capacity for carrying or containing a biologically active material per unit length of the outer surface than the parts of the outer surface that are outside the rectangular portion. In the alternative, the rectangular portion may have a greater affinity for the biologically active material. The present invention is also directed to a method for delivering a biologically active material by inserting the above-mentioned medical device comprising the biologically active material in such a way that the rectangular portion is in direct contact with the body tissue in need of treatment.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] **FIG. 1** depicts a side view of a stent without non-structural elements in a cross-sectioned blood vessel. The stent is coated with a biologically active material.

[0017] **FIGS. 2A and 2B** depict cross sectional views of the stent and blood vessel of **FIG. 1** along line A-A and line B-B (shown in **FIG. 2A**), respectively. **FIGS. 2A and 2B** also show areas of body tissue having different concentration levels of the biologically active material.

[0018] **FIG. 3** depicts a side view of a stent with non-structural elements in a cross-sectioned blood vessel. The stent is coated with a biologically active material.

[0019] **FIG. 4A and 4B** depict cross sectional views of the stent and blood vessel of **FIG. 3** along line C-C and line D-D (shown in **FIG. 4A**), respectively. **FIGS. 4A and 4B** also show areas having different concentration levels of the biologically active material.

[0020] **FIG. 5** depicts struts of a conventional expandable stent. FIGS. **6-14**, each depicts struts having non-functional elements integral with the struts.

[0021] FIG. 15 depicts wavy struts that have greater surface area per unit length of the strut than conventional struts.

[0022] FIG. 16 depicts struts having a greater average diameter per length of the strut than the conventional struts.

[0023] FIG. 17 depicts a simplified view of a stent having a rectangular portion of the outer surface where non-structural elements are located, and the rectangular portion is shown by hatching.

[0024] FIG. 18 depicts a perspective view of a stent wherein non-structural elements are located only in a rectangular portion of the outer surface.

[0025] FIG. 19 depicts a stent having end sections and a middle section and comprised of struts, wherein the end sections are comprised of a porous material and the middle section is comprised of a less porous material.

[0026] FIG. 20 is a simplified view of a stent which shows the outer surface, having end sections and a middle section.

DETAILED DESCRIPTION OF THE INVENTION

1. Medical Device for Delivering Biologically Active Material with Desired Distribution

[0027] 1.1 Non-Structural Elements

[0028] Even if a biologically active material having a pharmacological effect is delivered to a body tissue, such effect may not result if the concentration of the biologically active material in the body tissue is below a certain concentration (C_{min}). On the other hand, a biologically active material becomes toxic if its concentration is higher than a certain concentration (C_{max}). The concentration of the biologically active material at each and every area throughout the body tissue to be treated should be at or above C_{min} but at or under C_{max} of the biologically active material.

[0029] When the medical device is comprised of a plurality of struts comprising a biologically active material, the body tissue located at or near a center of each "cell" of the medical device, i.e., openings between the struts, tends to have the lowest concentration of the biologically active material. Such concentration can be below C_{min}. This is particularly true when the biologically active material is hydrophobic. When the concentration of the biologically active material in the tissue located at the center of each cell is lower than C_{min}, the concentration can be increased by increasing the amount of the biologically active material coated on outer surface of each strut. However, then the concentration at the tissue adjacent to the struts may exceed C_{max}.

[0030] For example, FIG. 1 depicts a coated stent 10 having a conventional geometric pattern, which is placed in a blood vessel 15 having a vessel wall 12 to be treated. The biologically active material coated on struts 13 of the stent 10 is released into the vessel wall 12 to be treated. FIGS. 2A and 2B show cross sectional views along line A-A and line B-B (shown in FIG. 2A) of the stent 10 in FIG. 1 and the concentration levels of the biologically active material in each area surrounding the struts 13 at a certain time after the stent 10 was inserted into the vessel 15. The area adjacent to the struts, i.e., the area between the struts 13 and line 16 has a concentration level at or below C_{max}, which is just below the toxic level. The farther from the struts 13 the area is located, the lower the concentration becomes. Thus, the concentration levels gradually decrease from the area between lines 16 and 17, the area between 17 and 18, to between 18 and 19. The area between line 18 and line 19 has a concentration level at or higher than C_{min}. A concentration of the biologically active material in the area outside line 19 is below C_{min}, and thus the pharmacological effects of the biologically active material does not result in the area.

[0031] Furthermore, FIGS. 2A and 2B clearly show that there are gaps between each strut 13, i.e., near the center of cells, wherein the vessel wall to be treated does not receive sufficient biologically active material to have C_{min}. The size of the area within line 19, i.e., the areas having the concentrations above C_{min}, may be increased to include the entire area of the vessel wall to be treated 12 if the amount of the biologically active material on the struts 13 is increased. However, by doing so, the area adjacent to the struts 13 may be also increased and exceed the toxic level. Therefore, there is a need for a medical device that can ensure the concentration of the biologically active material throughout the body tissue to be treated is at least C_{min} and at most C_{max}.

[0032] To achieve such a desired distribution of a biologically active material throughout the body tissue to be treated, the embodiments of the medical device of the present invention comprise a plurality of struts and a plurality of non-structural elements integral to the struts. The struts and non-structural elements comprise the biologically active material. These non-structural elements are used to adjust the distribution of the biologically active material in the body tissue so that the desired concentration-profile for the biologically active material released from the medical device into the body tissue can be achieved. For instance, the medical device of the present invention can achieve concentrations higher than C_{min} at the tissue located at the center of cells without increasing the local concentration at an area adjacent to the struts higher than C_{max}.

[0033] An example is shown in FIGS. 3, 4A and 4B. FIG. 3 depicts a coated stent 10' which is obtained by modifying the conventional geometric pattern of stent 10 shown in FIG. 1 by incorporating non-structural elements 14 integral to the struts 13. The stent 10' is placed in a blood vessel 15 having a vessel wall 12 to be treated. The biologically active material coated on struts 13 and non-structural elements 14 of the stent 10' is released into the vessel wall 12 to be treated and tissue 12a surrounding the vessel wall 12. FIGS. 4A and 4B show cross sectional views along line C-C and D-D (shown in FIG. 4A) of the stent 10' in FIG. 3 and the concentration levels of the biologically active material in each area surrounding the struts 13 and the nonstructural elements 14 at a certain time after the stent 10' was inserted in the vessel 15. The area adjacent to the struts, i. e., the area between the struts 13 or the nonstructural elements 14 and line 16 has a concentration level from at or below C_{max}, which is just below the toxic level. The farther from the struts 13 or the nonstructural elements 14 the area is located, the lower the concentration becomes. The area between line 18 and line 19 has the concentration level at or higher than C_{min}. FIG. 4 clearly shows that the stent 10' can achieve concentrations higher than C_{min} throughout the entire area of the vessel wall to be treated 12, even at areas located at the

center of cells, without increasing the concentration at areas adjacent to the struts above C_{max}.

[0034] The term "non-structural element" refers to an element integral with a strut, which can project from the strut or can be located along the strut. Such non-structural elements have substantially no effect on the mechanical properties of the struts, such as, for example, (1) radial strength, (2) longitudinal flexibility, (3) expansion ratio, (4) trackability and (5) profile of a medical device comprising the plurality of struts. In embodiments of the medical device of the present invention, the non-structural elements are integral with the struts, namely, they are generally made from the same material as the struts and are formed as a continuous part of the struts. Preferably, the non-structural elements and struts may be manufactured simultaneously; for example, struts having non-structural elements can be laser-ablated from a plate of metal or polymer.

[0035] **FIG. 5** depicts example of conventional struts without non-structural element, and FIGS. **6-14** depict examples of non-structural elements integral with the conventional struts. Shapes of the non-structural elements include, but not limited to, a straight rod (**21** in **FIG. 6**), a cone (**22** in **FIG. 7**), a truncated cone (not shown), a hoop (**23** in **FIG. 8**), a knot (**24** in **FIG. 9**), a bent rod (**25** in **FIG. 10**), an oval (**26** in **FIG. 11**), and a rod having beads at its ends (**27** in **FIG. 12** and **28** in **FIG. 13**). Bends in the struts (**29***a* and **29***b* in **FIG. 14**) can be used as non-structural elements so long as they do not affect the mechanical properties of the struts.

[0036] This embodiment of the medical device of the present invention can be used for delivering any kind of biologically active material. Preferably, the biologically active material is hydrophobic, e.g., paclitaxel, actinomycin, sirolimus, tacrolimus, everolimus, dexamethasone, halofuginone and hydrophobic nitric oxide adducts. Other examples of the biologically active material, coatings containing the biologically active material, and examples of the medical device are explained later in this application.

[0037] 1.2 Designing Medical Devices Having Struts and Non-Structural Elements

[0038] The present invention is directed to a method for designing a medical device comprising a plurality of struts and non-structural elements integral with the struts for delivering a biologically active material to a body tissue of a patient. As explained above, when the struts are placed in a certain geometric pattern, the concentration of a biologically active material at a center of each cell may not reach C_{min} of the biologically active material. However, the method of the present invention provides a geometric pattern of the struts in which the concentration of a biologically active material above C_{min} can be achieved throughout the body tissue to be treated without increasing the concentration at the tissue located adjacent to the struts above C_{max}.

[0039] In the method of the invention, a preliminary medical device comprising a plurality of struts in a geometric pattern is modified by incorporating non-structural elements to the struts to improve the concentration-profile for the biologically active material released from the device to the body tissue to be treated. Any medical device comprising a plurality of struts in a geometric pattern, such as stent, can be used as a preliminary medical device for the method of the invention provided that the struts comprises a biologically active material.

[0040] In the method of the present invention, a concentration-profile for the biologically active material delivered to the body tissue from the preliminary medical device is determined. From this profile, the areas of tissue in which the concentration of the biologically active material is below C_{min} can be determined. Such areas are then correlated to the parts of the geometric pattern of the struts of the preliminary medical device that were in contact with or near such areas.

[0041] The determination of such concentration-profile can be conducted by actually measuring concentrations using the biologically active material in vitro with a tissue model, which is similar to the body tissue to be treated, such as cannulated animal arteries with surrounding tissue or an artificial tissue, or in vivo with an animal model, such as rabbits or pigs. The biologically active material used for the experiment may be labeled with a fluorescence, a radioactive material or dye. Such labeled biologically active material is coated on the medical device, and then the coated medical device is inserted into the tissue model, or artificial tissue, or implanted in an animal. Alternatively, the biologically active material may be detected using standard GLP separation, mass spectroscopy or other direct analytical methods. After insertion, the tissue may be appropriately sectioned, and the concentration-profile for the labeled biologically active material is measured by a means appropriate to the label employed for the experiment. However, a necessary care should be taken that the label would not greatly affect the diffusion of the biologically active material itself.

[0042] However, the concentration-profile may also be determined by mathematical simulation. For example, assuming a simple diffusion model, such simulation can be conducted by using the following conditions and equations:

$$\frac{\partial C}{\partial t} = D_x\left(\frac{\partial^2 C}{\partial x^2}\right) + D_z\left(\frac{\partial^2 C}{\partial z^2}\right)$$

[0043] wherein C refers to a concentration of the biologically active material in the body tissue, x refers to a distance from the medical device along x axis which is perpendicular to a boundary between the medical device and the body tissue, z refers to a distance from the medical device along z axis which is parallel to the boundary, Dx refers to a diffusion coefficient of the biologically active material in direction along x axis, Dz refers to a diffusion coefficient of the biologically active material in a direction along z axis. For example, such x axis and z axis are shown in **FIGS. 1, 2B, 3** and **4B**. Dx and Dz can be determined by the experiments using the labeled biologically active material in vitro or in vivo as described above. C=0 at t=0, wherein boundary conditions are as follows:

[0044] (i) at a common boundary between the struts and the body tissue (at x=0):

$$D_x\frac{\partial C}{\partial x} = h_1(C - C_T)$$

[0045] wherein C_T refers to a concentration of the biologically active material in the struts, and h_1 refers to a mass

transfer coefficient. Value of h_1 can be determined by the same experiments described above or determined by assumption based on the information known to one skilled in the art,

[0046] (ii) at a boundary between blood flow and the body tissue (at x=0):

$$D_x \frac{\partial C}{\partial x} = h_2(C - 0)$$

[0047] wherein h_2 refers to another mass transfer coefficient. Value of h_2 can be determined by the same experiment mentioned above or determined by assumption based on the information known to one skilled in the art;

[0048] (iii) at an adventitial side of vascular wall (at x=L):

$$D_x \frac{\partial C}{\partial x} = -h_3(C - 0)$$

[0049] wherein h_3 is yet another mass transfer coefficient, and L is a width of a region of interest. Value of h_3 can be determined by the same experiment mentioned above or determined by assumption based on the information known to one skilled in the art; and

[0050] (iv) "symmetry" (no-flux) boundary conditions at certain cross-sections perpendicular to z axis:

$$\frac{\partial C}{\partial z}(z = 0) = \frac{\partial C}{\partial z}(z = L_z) = 0$$

[0051] wherein Lz is the length along z axis of a region of interest.

[0052] Although a simplified model based on two diffusion coefficients of the biologically active material in two directions, i.e., depth of the tissue penetration and the distance diffused, is described above as an example, there are more complex models can be also employed for the method of the present invention. Such complex models may further account for other variables, such as convection, vessel wall inhomogeneties, the type of cells, the lesions, the variabilities brought by different coatings or coating porosity, blood flow, body temperature, blood pressure, and/or pressure of the implant against the vessel wall.

[0053] Subsequent to determining the concentration-profile for the biologically active material which is released from the preliminary medical device, the geometric pattern of the preliminary medical device is modified by incorporating a plurality of non-functional elements that are integral with the struts to achieve more desired distribution of the biologically active material in the body tissue to be treated. The non-structural elements also comprise the biologically active material. For example, the area of tissue in which the concentration of the biologically active material is below C_{min} is determined from the concentration-profile. Then, it is determined which parts of the geometric pattern of the struts of the preliminary medical device were in contact with or near such areas. The non-structural elements can be incorporated near such parts in the geometric pattern, so that the biologically active material released from the non-structural elements would change the concentration in those areas.

[0054] For example, a stent **10** having a plurality of struts **13** in a conventional geometric pattern in **FIG. 1** can be provided as the preliminary medical device. The struts **13** are coated with a biologically active material. Then, a concentration-profile in a body tissue for the biologically active material which is released from the struts **13** is determined. An example of such profile is shown in **FIGS. 2A and 2B** with the cross-sectional views of the stent **10** in the blood vessel **15**. The determination of such concentration-profile can be conducted by actually measuring concentrations or by mathematical simulation as mentioned above. According to the obtained concentration-profile, the geometric pattern of the struts **13** of the preliminary stent **10** are modified with non-structural elements **14**, for example, as shown in **FIG. 3**. **FIGS. 4A and 4B** show the concentration-profile views for the biologically active material in the blood wall **12**. When the concentration-profile in the vessel wall to be treated **12** shown in FIGS. 2A-B and 4A-B are compared, in FIGS. 4A-B, the concentrations generally throughout the entire area of the vessel wall to be treated **12** are above C_{min} and below C_{max}. It is clear that the modified stent **10'** achieves a more desirable concentration-profile in the vessel to be treated **12** with the biologically active material than the preliminary stent **10**.

[0055] Preferably, after a concentration-profile for the biologically active material in the body tissue which is released from the modified preliminary medical device is determined, if there is an area of the body tissue having the local concentration of the biologically active material lower than C_{min}, then the device is modified again by adding non-structural elements to the struts. In addition to or instead of merely adding additional non-structural elements, the non-structural elements which have been already added can be removed or relocated according to the determined concentration-profile. Consequently, a medical device having further improved delivery of the biologically active material is obtained. If necessary, the determination step and the modification step explained above can be repeated as many as possible.

[0056] 1.3 Medical Device with Radially Asymmetric Area Having Non-Structure Elements

[0057] The prior sections (section 1.1 and 1.2) explained how non-structural elements can be added to a preliminary medical device to achieve a more desired concentration-profile for the biologically active material released from the device into body tissue. When the entire outer surface of a medical device, which comprises the plurality of struts and non-structural elements, is used to treat body, the non-structural elements should be positioned uniformly throughout the entire outer surface of the medical device.

[0058] However, if the body tissue to be treated is smaller in surface area than the entire outer surface of the medical device, then the non-structural elements do not have to be positioned throughout the entire surface of the medical device. For example, the medical device can comprise a tubular portion comprising an outer surface, such as a stent, which comprises a plurality of struts and a plurality of

non-structural elements. The non-structural elements located in a radially asymmetric distribution, such as shown in **FIG. 17** where **33** represents the location of the non-structural element on outer surface of a simplified figure of a stent **32**. In this figure, the non-structural elements are distributed only in a rectangular portion of the outer surface. **FIG. 18** depicts a perspective view of a stent wherein non-structural elements are provided onto the struts only in a rectangular portion of the outer surface. Such rectangular portion may be parallel to longitudinal axis of the tubular portion and may have the same length as that of the tubular portion. The rectangular portion is preferably from about 25% to about 75% of the entire outer surface.

[0059] The present invention is also directed to a method for delivering a biologically active material to body tissue using the above-mentioned medical device, which comprises a tubular portion comprising an outer surface which comprises a plurality of struts and a plurality of non-structural elements, and the non-structural elements are located in a radially asymmetric distribution on the outer surface. In the method, the medical device is inserted into body of the patient. Preferably, the non-structural elements are distributed only in a rectangular portion of the outer surface, and the medical device is inserted in such a way that the rectangular portion is in direct contact with the body tissue to be treated. In this way, the body tissue to be treated will receive desired distribution of the biologically active material. On the other hand, the body tissue which does not need to be treated will be exposed to a lesser amount of the biologically active material.

2. Increase Capacity of the End Sections for Carrying or Containing a Biological Active Material

[0060] In other embodiments of the medical device insertable into the body of a patient of the invention, the medical device comprises an outer surface comprising a plurality of struts, and the end sections of the outer surface have a greater capacity per unit length of the outer surface for carrying or containing a biologically active material than the middle section of the outer surface. Specifically, in one embodiment of the medical device, each strut at the end sections has greater available surface area per unit length of the outer surface than the middle section. In another embodiment, the end sections have a greater affinity for the biologically active material per unit length of the outer surface than the middle section.

[0061] The medical device of the present invention may be manufactured with or without a biologically active material by a manufacturer. When the medical device of the present invention is manufactured without a biologically active material, a practitioner (e.g., a medical doctor or a nurse) can apply the biologically active material to the medical device. In either case, since the end sections of the outer surface have a greater capacity per unit length of the outer surface for carrying or containing the biologically active material than the middle section, the end sections will carry a greater amount of the biologically active material when the biologically active material is applied to the medical device without needing to change application method of the biologically active material to the end sections and the method to the middle section. Therefore, when a practitioner applies to the outer surface of the medical device, such as by dipping, a coating composition containing a biologically active material, a larger amount of the biologically active material per unit length of the outer surface will be deposited at the end sections than the middle section.

[0062] The term "unit length of the outer surface" refers to the length on an imaginary straight line along the outer surface drawn between a point on an edge of the outer surface and another point on the opposing edge of the outer surface. Therefore, the terms, such as "capacity per unit length of the outer surface,""available surface area per unit length of the outer surface," and "amount per unit length of the outer surface," refer respectively to the capacity, available surface area and amount per unit length of the imaginary straight line explained above.

[0063] 2.1 Increase Available Surface Area at the End Sections

[0064] As explained above, one of the embodiments of the medical device has end sections which have greater available surface area per unit length of the outer surface than that of the middle section. The term "available surface area" refers to a surface area which is available to be coated by a coating composition comprising a biologically active material.

[0065] One way of increasing the available surface area of the end sections is to fabricate the outer surface of the medical device using more material at its ends. For example, when the medical device is comprised of struts, the available surface area per unit length of the outer surface in the end sections is increased by adding non-structural elements to the struts. The non-structural elements are explained above (see section 1.1). The end sections comprise a greater number of the non-structural elements per unit length of the outer surface than the middle section. The middle section may have smaller number of the non-structural elements or no non-structural elements.

[0066] Further, the available surface area can be increased by increasing the surface area of the struts themselves. For example, wavy struts **30** shown in **FIG. 15** can have more outer surface area per length than straight struts show in **FIG. 5**. Also, struts having greater average diameter, such as struts which are thicker or wider at certain portion **31** shown in **FIG. 16**, have greater outer surface area per length than struts which have smaller average diameter. Moreover, the end sections of the outer surface can be made to have greater available surface area by roughing the struts' outer surface or providing indentations or grooves on the struts' surface. The above-mentioned wavy struts, wider or thicker struts, indentations and grooves may have various shapes, so long as such structure does not affect stent's structural functions. For example, the above-mentioned structure should not hinder self-expansion of a self-expanding stent and should not cause any harm to the patient body. The above-mentioned wavy struts, indentations and grooves can be manufactured by laser ablation.

[0067] In another embodiment in which the capacity of the end sections to carry or contain the biologically active material is greater than the capacity of the middle section, the end sections of the outer surface are more porous, and the middle section of the surface is relatively less porous. The middle section may also be non-porous. For example, in **FIG. 19**, the circles **45** and **47** show enlarged portions of the

outer surface of the struts **42** of a stent **40** in the middle section **44** and end section **46**, respectively. The surface of the struts in the end section **46** has more pores **48** than the surface of the struts at the middle section **44**. In such embodiment, the end sections **46** have a greater available surface area per unit length of the outer surface than that of the middle section **44** since the pores **48** increase available surface area.

[0068] The end sections of the outer surface may be made porous by forming the end sections of the outer surface themselves from a porous material or by forming the end sections with a non-porous material and then covering the end sections with a porous coating layer. For example, porous metal struts can be prepared by sintering metal, ie., molding or pressing metal particles into a desired shape and heating them to a temperature slightly below the melting point of the metal. Porosity can be changed by using different particle sizes and/or dimensions and/or different temperatures. Also, porous metal struts can be prepared by using metal filaments or fibers. See e.g. U.S. Pat. No. 5,843,172 issued to Yan which discloses examples of struts made of porous materials, which is incorporated herewith by reference.

[0069] The end sections of the outer surface may be made porous by coated with a porous coating layer. A porous coating layer may be prepared, for example, by applying a mixture of a polymer, an elutable particulate material and a solvent on a surface to form a layer, and then eluting the elutable particulate material from the layer. The following is a detailed description of suitable materials and methods useful in producing a porous coating layer of the invention.

[0070] Polymer(s) useful for forming the porous coating layer should be ones that are biostable, biocompatible, particularly during insertion or implantation of the device into the body and avoids irritation to body tissue. Examples of such polymers include, but not limited to, polyurethanes, polyisobutylene and its copolymers, silicones, and polyesters. Other suitable polymers include polyolefins, polyisobutylene, ethylene-alphaolefin copolymers, acrylic polymers and copolymers, vinyl halide polymers and copolymers such as polyvinyl chloride, polyvinyl ethers such as polyvinyl methyl ether, polyvinylidene halides such as polyvinylidene fluoride and polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics such as polystyrene, polyvinyl esters such as polyvinyl acetate; copolymers of vinyl monomers, copolymers of vinyl monomers and olefins such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, ethylene-vinyl acetate copolymers, polyamides such as Nylon **66** and polycaprolactone, alkyd resins, polycarbonates, polyoxyethylenes, polyimides, polyethers, epoxy resins, polyurethanes, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, carboxymethyl cellulose, collagens, chitins, polylactic acid, polyglycolic acid, and polylactic acid-polyethylene oxide copolymers. Since the polymer is being applied to a part of the medical device which undergoes mechanical challenges, e.g. expansion and contraction, the polymers are preferably selected from elastomeric polymers such as silicones (e.g. polysiloxanes and substituted polysiloxanes), polyurethanes, thermoplastic elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers, and EPDM rubbers. The polymer is selected to allow the coating to better adhere to the surface of the expandable portion of the medical device when it is subjected to forces or stress. Furthermore, although the porous coating layer can be formed by using a single type of polymer, various combinations of polymers can be employed.

[0071] The elutable particulate materials which can be incorporated into the polymer include, but not limited to, polyethylene oxide, polyethylene glycol, polyethylene oxide/polypropylene oxide copolymers, polyhydroxyethyl methacrylate, polyvinylpyrrolidone, polyacrylamide and its copolymers, salts, e.g., sodium chloride, sugars, and elutable biologically active materials such as heparin. The amount of elutable particulate material that is incorporated into the polymer should range from about 20% to 90% by weight of the porous coating layer. Furthermore, to increase the porosity of the coating layer applied to the end sections of the surface, a larger amount of the elutable particulate material can be used to form the porous coating layer at the end sections than are used to form the porous coating layer at the middle section. For example, the amount of the elutable particulate material may be from about 0% to about 40% for the porous coating layer covering the middle section, and about 50% to 90% for the porous coating layer covering at the end sections. Also, a more porous coating layer can be realized by using larger average particle size of the elutable material. For example, the particles may have an average particle size from **60-100** microns for porous coating layer covering the end sections and from 0 to about 30 microns for the porous coating layer covering middle section.

[0072] The solvent that is used to form the mixture or slurry of polymer and elutable particulate materials include ones which can dissolve the polymer into solution and do not alter or adversely impact the therapeutic properties of the biologically active material employed. Examples of useful solvents for silicone include tetrahydrofuran (THF), chloroform and dichloromethane. The composition of polymer and elutable particulate material can be applied to the portion of the medical device in a variety of ways. For example, the composition can be spray-coated onto the device or the device can be dipped into the composition. One of skill in the art would be aware of methods for applying the coating to the device.

[0073] The thickness of the porous coating layer can range from about 25 μm to 0.5 mm. Preferably, the thickness is about 30 μm to 100 μm. After the composition is applied to the device, it should be cured to produce a polymer containing the particulate material and to evaporate the solvent.

[0074] To elute the particulate material from the polymer, a solvent is used. The device can be soaked in the solvent to elute the particulate materials. Other methods of eluting the particulate are apparent to those skilled in the art. The choice of the solvent depends upon the solubility of the elutable particulate material in that solvent. For instance, for water-soluble particulate materials such as heparin, water can be used. For elutable particulate materials that can be dissolved in organic solvents, such organic solvents can be used. Examples of suitable solvents, without limitation, include ethanol, dimethyl sulfoxide, etc.

[0075] Another example of a method for preparing a porous coating is a catalyst-free vapor deposition of a coating composition comprising a polyamide, parylene or a

parylene derivative. See U.S. Pat. No. 6,299,604 to Ragheb et al., which is incorporated herein by reference.

[0076] In another embodiment of the present invention, the surface including the end sections and middle section are covered with a same porous coating layer composition; but the porous coating layer is thicker at the end sections than at the middle section. For example, a porous coating layer is applied to the entire surface, and then another porous coating layer is applied to the end sections while the middle section is covered by a sheath. The thickness of the porous coating layer at the end sections may be from about 80 μm to about 0.5 mm, and that at the middle section may be from about 10 μm to 40 μm. Since there is more porous coating at the end sections, the end sections of the outer surface should have a greater capacity to carry or contain a biologically active material.

[0077] 2.2 The End Sections with Greater Affinity for the Biological Active Material

[0078] In another embodiment of the medical device of the present invention, the end sections of the outer surface have a greater affinity for the biologically active material than the middle section. In particular, the end sections comprise a first matrix material and the middle section comprises a second matrix material. The first matrix material has a greater affinity for the biologically active material of interest than the second matrix material so that the end sections can carry or contain a larger amount of the biologically active material per unit length of the outer surface than the middle section. The end sections and the middle section of the outer surface may be formed from the first matrix material and the second matrix material, respectively. Preferably, the end sections of the outer surface and the middle section of the outer surface are formed of another material and then are covered with a coating comprising each of the matrix materials.

[0079] Generally, when a biologically active material used is a hydrophilic, e.g., heparin, then a matrix material comprising a more hydrophilic material has a greater affinity for the biologically active material than another matrix material that is less hydrophilic. When a biologically active material used is a hydrophobic, e.g., paclitaxel, actinomycin, sirolimus (RAPAMYCIN), tacrolimus, everolimus, and dexamethasone, then a matrix material that is more hydrophobic has a greater affinity for the biologically active material than another matrix material that is less hydrophobic.

[0080] Examples of suitable hydrophobic polymers include, but not limited to, polyolefins, such as polyethylene, polypropylene, poly(1-butene), poly(2-butene), poly(1-pentene), poly(2-pentene), poly(3-methyl-1-pentene), poly(4-methyl- 1-pentene), poly(isoprene), poly(4-methyl-1-pentene), ethylene-propylene copolymers, ethylene-propylene-hexadiene copolymers, ethylene-vinyl acetate copolymers, blends of two or more polyolefins and random and block copolymers prepared from two or more different unsaturated monomers; styrene polymers, such as poly(styrene), poly(2-methylstyrene), styrene-acrylonitrile copolymers having less than about 20 mole-percent acrylonitrile, and styrene-2,2,3,3,-tetrafluoropropyl methacrylate copolymers; halogenated hydrocarbon polymers, such as poly(chlorotrifluoroethylene), chlorotrifluoroethylene-tetrafluoroethylene copolymers, poly(hexafluoropropylene), poly(tetrafluoroethylene), tetrafluoroethylene, tetrafluoroethylene-ethylene copolymers, poly(trifluoroethylene), poly(vinyl fluoride), and poly(vinylidene fluoride); vinyl polymers, such as poly(vinyl butyrate), poly(vinyl decanoate), poly(vinyl dodecanoate), poly(vinyl hexadecanoate), poly(vinyl hexanoate), poly(vinyl propionate), poly(vinyl octanoate), poly(heptafluoroisopropoxyethylene), poly(heptafluoroisopropoxypropylene), and poly(methacrylonitrile); acrylic polymers, such as poly(n-butyl acetate), poly(ethyl acrylate), poly(1-chlorodifluoromethyl)tetrafluoroethyl acrylate, poly di(chlorofluoromethyl)fluoromethyl acrylate, poly(1,1-dihydrohexafluorobutyl acrylate), poly(1,1-dihydropentafluoroisopropyl acrylate), poly(1,1-dihydropentadecafluorooctyl acrylate), poly(heptafluoroisopropyl acrylate), poly 5-(heptafluoroisopropoxy)pentyl acrylate, poly 11-(heptafluoroisopropoxy)undecyl acrylate, poly 2-(heptafluoropropoxy-)ethyl acrylate, and poly(nonafluoroisobutyl acrylate); methacrylic polymers, such as poly(benzyl methacrylate), poly(n-butyl methacrylate), poly(isobutyl methacrylate), poly(t-butyl methacrylate), poly(t-butylaminoethyl methacrylate), poly(dodecyl methacrylate), poly(ethyl methacrylate), poly(2-ethylhexyl methacrylate), poly(n-hexyl methacrylate), poly(phenyl methacrylate), poly(n-propyl methacrylate), poly(octadecyl methacrylate), poly(1,1-dihydropentadecafluorooctyl methacrylate), poly(heptafluoroisopropyl methacrylate), poly(heptadecafluorooctyl methacrylate), poly(1-hydrotetrafluoroethyl methacrylate), poly(1,1-dihydrotetrafluoropropyl methacrylate), poly(1-hydrohexafluoroisopropyl methacrylate), and poly(1-nonafluorobutyl methacrylate); polyesters, such a poly(ethylene terephthalate) and poly(butylene terephthalate); condensation type polymers such as and polyurethanes and siloxane-urethane copolymers; polyorganosiloxanes, i.e., polymeric materials characterized by repeating siloxane groups, represented by $R_x SiO_{4-x/2}$, where R is a monovalent substituted or unsubstituted hydrocarbon radical and the value of a is 1 or 2; and naturally occurring hydrophobic polymers such as rubber.

[0081] Examples of suitable hydrophilic monomer include, but not limited to; (meth)acrylic acid, or alkaline metal or ammonium salts thereof; (meth)acrylamide; (meth-)acrylonitrile; those polymers to which unsaturated dibasic, such as maleic acid and fumaric acid or half esters of these unsaturated dibasic acids, or alkaline metal or ammonium salts of these dibasic adds or half esters, is added; those polymers to which unsaturated sulfonic, such as 2-acrylamido-2-methylpropanesulfonic, 2-(meth)acryloylethanesulfonic acid, or alkaline metal or ammonium salts thereof, is added; and 2-hydroxyethyl (meth)acrylate and 2-hydroxypropyl (meth)acrylate. Polyvinyl alcohol is also an example of hydrophilic polymer. Polyvinyl alcohol may contain a plurality of hydrophilic groups such as hydroxyl, amido, carboxyl, amino, ammonium or sulfonyl (—SO_x). Hydrophilic polymers also include, but are not limited to, starch, polysaccharides and related cellulosic polymers; polyalkylene glycols and oxides such as the polyethylene oxides; polymerized ethylenically unsaturated carboxylic acids such as acrylic, mathacrylic and maleic acids and partial esters derived from these acids and polyhydric alcohols such as the alkylene glycols; homopolymers and copolymers derived from acrylamide; and homopolymers and copolymers of vinylpyrrolidone.

[0082] The first matrix material and the second matrix material may be prepared using either a hydrophilic polymer or a hydrophobic polymer, or a blend of a hydrophobic

polymer and a hydrophilic polymer in a chosen ratio. For example, when the biologically active material is hydrophilic, then the first matrix material may be prepared by blending from about 55% to about 100% hydrophilic polymer and from about 45% to about 0% hydrophobic polymer; and the second matrix material may be prepared by blending from about 55% to about 100% hydrophobic polymer and from about 45% to about 0% hydrophilic polymer. The first matrix material contains a greater amount of the hydrophillic polymer than the second matrix material. When the biologically active material is hydrophobic, then the first matrix material may be prepared by blending from about 55% to about 95% hydrophobic polymer and from about 45% to about 5% hydrophilic polymer; and the second matrix material may be prepared by blending from about 55% to about 95% hydrophilic polymer and from about 45% to about 5% hydrophobic polymer. The first matrix material contains a greater amount of the hydrophobic polymer than the second matrix material.

[0083] Again, the outer surface of the medical device of the present invention is, covered with each matrix material, i.e., the end sections with a first matrix material and the middle section with a second matrix material. A first matrix material composition may be prepared and applied by any method to a surface of a medical device to form a coating, such as spraying, dipping, rolling, and electrostatic deposition. Likewise, a second matrix material composition may be prepared and applied by such methods. The first matrix material composition may be applied to the end sections of the outer surface while the middle section is covered to prevent coating the middle section with the first matrix material. Then the second matrix material composition may be applied to the middle section while the end sections are covered. In another embodiment, the second material composition may be applied to the entire outer surface including the middle section and the end sections, then the first matrix material composition may be applied to the end sections while the middle section is covered.

[0084] After the matrix material compositions are applied to the outer surface, the surface should be cured to produce matrix material coatings. The thickness of the matrix material coating can range from about 25 μm to about 0.5 mm. Preferably, the thickness is about 30 μm to 100 μm.

[0085] 2.3 The End Sections with Greater Amount of Chemical Linking Material to Carry or Contain the Biological Active Material

[0086] In yet another embodiment of the present invention, the capacity of the end sections of the outer surface for carrying or containing a biologically active material can be increased relative to that of the middle section by using an increased amount of chemical linking material to link the biologically active material to the end sections of the outer surface. Specifically, the middle section and end sections of the outer surface are covered with a chemical linking material, and the end sections carry or contain a larger amount of the linking material per unit length of outer surface than the middle section. The chemical linking material allows the biologically active material to attach to the outer surface. "Linking materials" may be any material which can be coupled to a biologically active material by any bond that are known in the relevant art including but not limited to, Van der Waals force, ionic bond, covalent bond, hydrogen bond or chemical cross-linking.

[0087] For example, U.S. Pat. No. 5,356,433 to Rowland et al., discloses that polysaccharides can be immobilized onto metallic surfaces by applying an organosilane coating with amine functionality and then applying a polysaccharide using carbodiimide as a coupling agent. In the present invention, if the organosilane with amine functionality is used as a linking material, the amount of this material per unit length of the outer surface at the end sections is greater than that at the middle section. In that way, larger amount of a polysaccharide, which is a biologically active material, can coupled to the end sections.

[0088] Also, U.S. Pat. No. 5,336,518 to Narayanan et al. discloses that a polysaccharide can be immobilized on a surface by applying a coat of heptafluorobutylmethacrylate (HFBMA) by radiofrequency (RF) plasma deposition, creating functional groups on the surface by RF plasma with water vapor, and then applying the polysaccharide using carbodiimide. In the present invention, larger amount of HFBMA, a linking material, is applied to the end sections so that larger amount of a polysaccharide, a biologically active material can be coupled to.

3. Radially Asymmetric Medical Devices Having Increased Capacity for Carrying or Containing a Biologically Active Material

[0089] 3.1 Medical Devices Having Non-Structural Elements Located in a Radially Asymmetric Distribution

[0090] As explained above, one way to increase the capacity for carrying or containing a biologically active material of the medical device is to increase available surface area. In one embodiment of the medical device of the invention, the available surface area is increased in radially asymmetric manner along the entire outer surface, instead of only at the end sections. One such embodiment where the surface area is increased in a radially asymmetric manner by adding non-structural elements to the outer surface (as to non-structural elements, see section 1.3). For example, only a rectangular portion of the outer surface has the non-structural elements. Such rectangular portion may be parallel to longitudinal axis of the tubular portion and may have the same length as that of the tubular portion. The rectangular portion is preferably from about 25% to about 75% of the entire outer surface. Please see section 1.3 as to a method for delivering a biologically active material to body tissue using such medical device.

[0091] 3.2 Medical Device Having Radially Asymmetric Increased Available Surface Area or Affinity

[0092] Another embodiment of the medical device of the invention comprises a tubular portion comprising struts and having an outer surface. A portion of the outer surface has increased available surface or affinity for the biologically active material in such a way that the available surface area or affinity for the biologically active material is radially asymmetric. Please see prior section (section 3.1) as to examples of radially asymmetric distributions. Increased available surface area or increased affinity to the biologically active material can be achieved as explained in the prior sections (sections 2.1 and 2.2). Please see section 1.3 as to a method for delivering a biologically active material to body tissue using such medical device.

4. Suitable Medical Devices

[0093] The medical devices of the present invention are insertable into the body of a patient. Namely, at least a

portion of such medical devices may be temporary inserted into or semi-permanently or permanently implanted in the body of a patient. Preferably, the medical devices of the present invention comprise a tubular portion which is insertable into the body of a patient. The tubular portion of the medical device need not to be completely cylindrical. For instance, the cross-section of the tubular portion can be any shape, such as rectangle, a triangle, etc., not just a circle.

[0094] The medical devices suitable for the present invention include, but are not limited to, stents, surgical staples, catheters, such as central venous catheters and arterial catheters, guidewires, balloons, filters (e.g., vena cava filters), cannulas, cardiac pacemaker leads or lead tips, cardiac defibrillator leads or lead tips, implantable vascular access ports, stent grafts, vascular grafts or other grafts, interluminal paving system, intra-aortic balloon pumps, heart valves, cardiovascular sutures, total artificial hearts and ventricular assist pumps.

[0095] Medical devices which are particularly suitable for the present invention include any kind of stent for medical purposes, which are known to the skilled artisan. Suitable stents include, for example, vascular stents such as self-expanding stents and balloon expandable stents. Examples of self-expanding stents useful in the present invention are illustrated in U.S. Pat. Nos. 4,655,771 and 4,954,126 issued to Wallsten and U.S. Pat. No. 5,061,275 issued to Wallsten et al. Examples of appropriate balloon-expandable stents are shown in U.S. Pat. No. 4,733,665 issued to Palmaz, U.S. Pat. No. 4,800,882 issued to Gianturco, U.S. Pat. No. 4,886,062 issued to Wiktor and U.S. Pat. No. 5,449,373 issued to Pinchasik et al. A bifurcated stent is also included among the medical devices suitable for the present invention.

[0096] The medical devices suitable for the present invention may be fabricated from polymeric and/or metallic materials. Examples of such polymeric materials include polyurethane and its copolymers, silicone and its copolymers, ethylene vinyl-acetate, poly(ethylene terephthalate), thermoplastic elastomer, polyvinyl chloride, polyolephines, cellulosics, polyamides, polyesters, polysulfones, polytetrafluoroethylenes, acrylonitrile butadiene styrene copolymers, acrylics, polyactic acid, polyclycolic acid, polycaprolactone, polyacetal, poly(lactic acid), polylactic acid-polyethylene oxide copolymers, polycarbonate cellulose, collagen and chitins. Examples of suitable metallic materials include metals and alloys based on titanium (e.g., nitinol, nickel titanium alloys, thermo-memory alloy materials), stainless steel, platinum, tantalum, nickel-chrome, certain cobalt alloys including cobalt-chromium-nickel alloys (e.g., Elgiloy® and Phynox®) and gold/platinum alloy. Metallic materials also include clad composite filaments, such as those disclosed in WO 94/16646.

[0097] The medical devices suitable for the present invention also have an outer surface, and the outer surface has end sections and middle section. The term "outer surface" refers to a surface of the medical devices which are to be exposed to body tissue. For example, the tubular structure shown in **FIG. 20** is a simplified view of a stent **40**. The outer surface of the stent is the surface that is in direct contact with the body tissue when the device is inserted into the body. In the case that the medical device is a stent **40** comprised of struts **42** as shown in **FIG. 19**, the "outer surface" of the stent refers to the surfaces of the struts which are to directly contact with the body lumen or tissue.

[0098] The term "end section" of the outer surface refers to that part of the surface which extends from an end or edge of the tubular portion up to about 25%, preferably from about 3% to about 20% of the entire length of the outer surface. For example, when the medical device is a stent **40** as shown in **FIG. 19** or **20**, the end section **46** of the outer surface is a ring-shape portion extending from the edge of the outer surface of stent having length e, which is up to 25% of the entire length α of the outer surface of stent. In **FIGS. 19 and 20**, the end sections are shown as the shaded portions **46**.

[0099] The term "middle section" refers to the remainder of the outer surface that is surrounded by the end sections as defined above. For example, in **FIG. 19** or **20**, the middle section **44** is a ring-shape portion having length m, which is surrounded by the end sections.

5. Applying Biologically Active Material to the Outer Surface

[0100] As discussed earlier, the biologically active material can be applied to the embodiments described in sections 2.1 to 2.3 when the device is manufactured or later on by a medical professional shortly before the device is inserted into a patient. The biologically active material may be applied to the outer surface of the device obtained as in sections 1.1-**1.3, 2.1-2.3** and **3.1-3.2**, alone or in conjunction with other materials, such as a polymeric material. For example, in the embodiment where the end sections have a greater available surface area per unit length of the outer surface than the middle section, the biologically active material can be applied to the outer surface in a coating composition containing the biologically active material and a polymeric material. Specifically, a coating composition of biologically active material and polymeric material can be prepared and then applied to the outer surface. However, the biologically active material alone can also be applied to the outer surface of this embodiment.

[0101] In the embodiments where a portion of the outer surface has a greater affinity for the biologically active material or where a portion of the outer surface contains more chemical liking material, the biologically active material is preferably applied alone to the outer surface. For instance, in the embodiment having a matrix material with greater affinity for the biologically active material in a portion of the outer surface, the biologically active material can be applied to the matrix material coatings on the outer surface. However, the biologically active material can also be applied to the material along with a polymeric material. Also, the biologically active material can be incorporated into the matrix material coating compositions to form matrix material coatings that already containing biologically active material.

[0102] 5.1 Coating Compositions and Coating Layers

[0103] The coating compositions suitable for the present invention can be applied by any method to a surface of a medical device to form a coating. Examples of such methods are spraying, dipping, rolling, electrostatic deposition and all modern chemical ways of immobilization of bio-molecules to surfaces.

[0104] The coating composition used in the present invention may be a solution of a biologically active material in an

aqueous or organic solvent. Such coating composition may be applied to a surface, and the solvent may be evaporated. A biologically active material solution may be used when the tubular portion of the medical device has end sections having increased surface area or increased affinity as explained above, especially when the end sections are porous.

[0105] Furthermore, coating compositions useful for the present invention may include a polymeric material and optionally a biologically active material dispersed or dissolved in a solvent suitable for the medical device which is known to the skilled artisan. The solvents used to prepare coating compositions include ones which can dissolve the polymeric material into solution and do not alter or adversely impact the therapeutic properties of the biologically active material employed. For example, useful solvents for silicone include tetrahydrofuran (THF), chloroform, toluene, acetone, isooctane, 1,1,1-trichloroethane, dichloromethane, and mixture thereof.

[0106] A coating of a medical device of the present invention may consist of various kinds of combination of multiple coating layers. For example, the first layer and the second layer may contain different biologically active materials. Alternatively, the first layer and the second layer may contain an identical biologically active material having different concentrations. In one embodiment, either of the first layer or the second layer may be free of biologically active material. For example, when the biologically active solution is applied onto a surface and dried (the first layer), a coating composition free of a biologically active material (the second layer) can be applied over the dried biologically active material.

[0107] The polymeric material should be a material that is biocompatible and avoids irritation to body tissue. Examples of the polymeric materials used in the coating composition of the present invention include, but not limited to, polycarboxylic acids, cellulosic polymers, including cellulose acetate and cellulose nitrate, gelatin, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyanhydrides including maleic anhydride polymers, polyamides, polyvinyl alcohols, copolymers of vinyl monomers such as EVA, polyvinyl ethers, polyvinyl aromatics, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters including polyethylene terephthalate, polyacrylamides, polyethers, polyether sulfone, polycarbonate, polyalkylenes including polypropylene, polyethylene and high molecular weight polyethylene, halogenated polyalkylenes including polytetrafluoroethylene, polyurethanes, polyorthoesters, proteins, polypeptides, silicones, siloxane polymers, polylactic acid, polyglycolic acid, polycaprolactone, polyhydroxybutyrate valerate, styrene-isobutylene copolymers and blends and copolymers thereof. Also, other examples of such polymers include polyurethane (BAYHDROL®, etc.) fibrin, collagen and derivatives thereof, polysaccharides such as celluloses, starches, dextrans, alginates and derivatives, hyaluronic acid, and squalene. Further examples of the polymeric materials used in the coating composition of the present invention include other polymers which can be used include ones that can be dissolved and cured or polymerized on the medical device or polymers having relatively low melting points that can be blended with biologically active materials. Additional suitable polymers include, thermoplastic elastomers in general, polyolefins, polyisobutylene, ethylene-alphaolefin copolymers, acrylic polymers and copolymers, vinyl halide polymers and copolymers such as polyvinyl chloride, polyvinyl ethers such as polyvinyl methyl ether, polyvinylidene halides such as polyvinylidene fluoride and polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics such as polystyrene, polyvinyl esters such as polyvinyl acetate, copolymers of vinyl monomers, copolymers of vinyl monomers and olefins such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS (acrylonitrile-butadiene-styrene) resins, ethylene-vinyl acetate copolymers, polyamides such as Nylon 66 and polycaprolactone, alkyd resins, polycarbonates, polyoxymethylenes, polyimides, epoxy resins, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, carboxymethyl cellulose, collagens, chitins, polylactic acid, polyglycolic acid, polylactic acid-polyethylene oxide copolymers, EPDM (etylene-propylene-diene) rubbers, fluorosilicones, polyethylene glycol, polysaccharides, phospholipids, and combinations of the foregoing.

[0108] Preferred is polyacrylic acid, available as HYDROPLUS® (Boston Scientific Corporation, Natick, Mass.), and described in U.S. Pat. No. 5,091,205, the disclosure of which is hereby incorporated herein by reference. In a most preferred embodiment of the invention, the polymer is a copolymer of polylactic acid and polycaprolactone.

[0109] More preferably for medical devices which undergo mechanical challenges, e.g. expansion and contraction, the polymeric materials should be selected from elastomeric polymers such as silicones (e.g. polysiloxanes and substituted polysiloxanes), polyurethanes, thermoplastic elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers, and EPDM rubbers. Because of the elastic nature of these polymers, the coating composition adheres better to the surface of the medical device when the device is subjected to forces, stress or mechanical challenge.

[0110] A controlled-release coating of a biologically active material may be prepared by a coating composition comprising an appropriate hydrophobic polymer. For example, a controlled-release coating may comprise a coating layer containing a biologically active material and a top coating layer comprising a hydrophobic polymer. Also, a controlled-release coating may be prepared from a coating composition containing a mixture of a hydrophobic polymer and a biologically active material.

[0111] The amount of the polymeric material present in the coatings can vary based on the application for the medical device. One skilled in the art is aware of how to determine the desired amount and type of polymeric material used in the coating. The thickness of the coating is not limited, but generally ranges from about 25 μm to about 0.5 mm. Preferably, the thickness is about 30 μm to 100 μm.

[0112] 5.2 Suitable Biologically Active Material

[0113] The term "biologically active material" encompasses therapeutic agents, such as drugs, and also genetic materials and biological materials. The genetic materials mean DNA or RNA, including, without limitation, of DNA/RNA encoding a useful protein stated below, anti-sense DNA/RNA, intended to be inserted into a human body including viral vectors and non-viral vectors. Examples of DNA suitable for the present invention include DNA encoding

[0114] anti-sense RNA

[0115] tRNA or rRNA to replace defective or deficient endogenous molecules

[0116] angiogenic factors including growth factors, such as acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet-derived endothelial growth factor, platelet-derived growth factor, tumor necrosis factor α, hepatocyte growth factor and insulin like growth factor

[0117] cell cele inhibitors including CD inhibitors

[0118] thymidine kinase ("TK") and other agents useful for interfering with cell proliferation, and

[0119] the family of bone morphogenic proteins ("BMP's") as explained below. Viral vectors include adenoviruses, gutted adenoviruses, adeno-associated virus, retroviruses, alpha virus (Semliki Forest, Sindbis, etc.), lentiviruses, herpes simplex virus, ex vivo modified cells (e.g., stem cells, fibroblasts, myoblasts, satellitic cells, pericytes, cardiomyocytes, skeletal myocytes, macrophage), replication competent viruses (e.g., ONYX-015), and hybrid vectors. Non-viral vectors include artificial chromosomes and mini-chromosomes, plasmid DNA vectors (e.g, pCOR), cationic polymers (e.g., polyethyleneimine, polyethyleneimine (PEI)) graft copolymers (e.g., polyether-PEI and polyethylene oxide-PEI), neutral polymers PVP, SP1017 (SUPRATEK), lipids or lipoplexes, nanoparticles and microparticles with and without targeting sequences such as the protein transduction domain (PTD).

[0120] The biological materials include cells, yeasts, bacteria, proteins, peptides, cytokines and hormones. Examples for peptides and proteins include growth factors (FGF, FGF-1, FGF-2, VEGF, Endothelial Mitogenic Growth Factors, and epidermal growth factors, transforming growth factor α and β, platelet derived endothelial growth factor, platelet derived growth factor, tumor necrosis factor α, hepatocyte growth factor and insulin like growth factor), transcription factors, proteinkinases, CD inhibitors, thymidine kinase, and bone morphogenic proteins (BMP's), such as BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, and BMP-16. Currently preferred BMP's are BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7. Alternatively or in addition, molecules capable of inducing an upstream or downstream effect of a BMP can be provided. Such molecules include any of the "hedgehog" proteins, or the DNA's encoding them. These dimeric proteins can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Cells can be of human origin (autologous or allogeneic) or from an animal source (xenogeneic), genetically engineered, if desired, to deliver proteins of interest at the transplant site. The delivery media can be formulated as needed to maintain cell function and viability. Cells include whole bone marrow, bone marrow derived mono-nuclear cells, progenitor cells (e.g., endothelial progenitor cells) stem cells (e.g., mesenchymal, hematopoietic, neuronal), pluripotent stem cells, fibroblasts, macrophage, and satellite cells.

[0121] Biologically active material also includes non-genetic therapeutic agents, such as:

[0122] anti-thrombogenic agents such as heparin, heparin derivatives, urokinase, and PPack (dextrophenylalanine proline arginine chloromethylketone);

[0123] anti-proliferative agents such as enoxaprin, angiopeptin, or monoclonal antibodies capable of blocking smooth muscle cell proliferation, hirudin, and acetylsalicylic acid, amlodipine and doxazosin;

[0124] anti-inflammatory agents such as glucocorticoids, betamethasone, dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, and mesalamine;

[0125] immunosuppressants such as sirolimus (RAPAMYCIN), tacrolimus, everolimus and dexamethasone,

[0126] antineoplastic/antiproliferative/anti-miotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, methotrexate, azathioprine, halofuginone, adriamycin, actinomycin and mutamycin; endostatin, angiostatin and thymidine kinase inhibitors, and its analogs or derivatives;

[0127] anesthetic agents such as lidocaine, bupivacaine, and ropivacaine;

[0128] anti-coagulants such as D-Phe-Pro-Arg chloromethyl keton, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, anti-thrombin anticodies, anti-platelet receptor antibodies, aspirin (aspirin is also classified as an analgesic, antipyretic and anti-inflammatory drug), dipyridamole, protamine, hirudin, prostaglandin inhibitors, platelet inhibitors and tick antiplatelet peptides;

[0129] vascular cell growth promotors such as growth factors, Vascular Endothelial Growth Factors (FEGF, all types including VEGF-2), growth factor receptors, transcriptional activators, and translational promotors;

[0130] vascular cell growth inhibitors such as anti-proliferative agents, growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin;

[0131] cholesterol-lowering agents; vasodilating agents; and agents which interfere with endogenous vasoactive mechanisms;

[0132] anti-oxidants, such as probucol;

[0133] antibiotic agents, such as penicillin, cefoxitin, oxacillin, tobranycin

[0134] angiogenic substances, such as acidic and basic fibrobrast growth factors, estrogen including estradiol (E2), estriol (E3) and 17-Beta Estradiol; and

[0135] drugs for heart failure, such as digoxin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors including captopril and enalopril.

[0136] Also, the biologically active materials of the present invention include nitric oxide adducts, which prevent and/or treat adverse effects associated with use of a medical device in a patient, such as restenosis and damaged blood vessel surface. Typical nitric oxide adducts include nitroglycerin, sodium nitroprusside, S-nitroso-proteins, S-nitroso-thiols, long carbon-chain lipophilic S-nitrosothiols, S-nitrosodithiols, iron-nitrosyl compounds, thionitrates, thionitrites, sydnonimines, furoxans, organic nitrates, and nitrosated amino acids, preferably mono-or poly-nitrosylated proteins, particularly polynitrosated albumin or polymers or aggregates thereof. The albumin is preferably human or bovine, including humanized bovine serum albumin. Such nitric oxide adducts are disclosed in U.S. Pat. No. 6,087,479 to Stamler et al. which is incorporated herein by reference.

[0137] A biologically active material may be encapsulated in micro-capsules by the known methods.

[0138] 5.3 Medical Devices with End Sections that Carry or Contain a Greater Amount of Biologically Active Material than the Middle Section

[0139] In another embodiment of the invention, a more uniform release-profile for a biologically active material along the length of the outer surface of the medical device may be achieved by preparing a medical device having end sections that carry or contain a greater amount of a biologically active material than the middle section.

[0140] In section 2, supra, the medical devices of the present invention having end sections that have increased capacity for carrying or containing a biologically active material were explained. When a coating composition comprising the biologically active material is applied to such medical devices by a conventional method, such as spraying, dipping, rolling, and electrostatic deposition, the end sections will carry or contain a greater amount of the biologically active material per unit length of the outer surface than the middle section of the outer surface.

[0141] However, greater amounts of biologically active material at the end sections can also be achieved by controlling the amount of the biologically active material that is applied to the middle and end sections. For instance, additional coating composition containing a biologically active material can be applied to the end sections so that such sections have a thicker coating and hence contain more biologically active material. A method for preparing such medical device comprises, for example, applying a first coating composition containing a biologically active material to the end sections and a middle section of an outer surface, placing a cover over the middle section, applying more of the first coating composition or second coating composition to the end sections of the outer surface. The second coating composition may contain the same biologically active material as the first coating composition having the same or different concentration or may contain a different biologically active material.

[0142] Another example of a method useful in allowing more biologically active material to the end sections relative to the middle section involves covering the middle section. In particular, a coating composition containing the desired biologically active material is applied to the middle section and end sections. The middle section is then covered by a sheath or mesh. Such covering can be achieved also by masking using photolithography techniques. Additional coating composition is then applied to the end sections. The covering prevents such additional coating composition from being applied to the middle section so that the end sections will contain relatively more biologically active material.

[0143] In yet another embodiment of the medical device of the present invention, a greater amount of biologically active material can be applied to the end sections by applying coating compositions having different concentration of first biologically active material to the middle and end sections. For example, applying a coating composition containing a first concentration of a biologically active material is applied to the end sections while the middle section is covered. Thereafter, a second coating composition having a second concentration of biologically active material, which is smaller than the first concentration, to the middle section. The sections may be covered using sheaths or masking as explained above.

[0144] 5.4 Medical Device Comprising a Biologically Active Material in a Radially Asymmetric Distribution

[0145] Yet another embodiment of the medical device of the invention achieves a greater amount of release of a biologically active material to a necessary body tissue. Such medical device comprises an outer surface comprising the biologically active material in a radially asymmetric distribution. For example, a rectangular portion of the outer surface has a greater amount of the biologically active material than the rest of the outer surface. When the medical device comprises a tubular portion, the rectangular portion may be parallel to longitudinal axis of the tubular portion. The rectangular portion may be the same length as that of the tubular portion. A greater amount of the biologically active material can be distributed to a rectangular portion using any of the manners used to distribute a greater amount of the biologically active material to the end sections (see section 5.3, supra).

6. Barrier Layer Over the Middle Section

[0146] In yet another embodiment, there is a barrier layer placed over the middle section of the outer surface, so that the end sections of the outer surface are allowed to release greater amounts of the biologically active material relative to the middle section. The middle and end sections are covered with a coating composition containing biologically active material. A covering or barrier layer is then placed over the middle section to limit the release of the biologically active material. In this way, the release ratio of biologically active material from the end sections is relatively greater than from the middle section.

[0147] Examples of such barrier layers include, but not limited to, a top-coating layer covering the middle section. When the medical device of the present invention is a stent, examples of such barrier layers include, but not limited to, a sheath with or without apertures or openings. Suitable material for making such barrier layer include, but not limited to, hydrophobic polymers listed in section 2.2, supra.

[0148] The description contained herein is for purposes of illustration and not for purposes of limitation. Changes and

modifications may be made to the embodiments of the description and still be within the scope of the invention. Furthermore, obvious changes, modifications or variations will occur to those skilled in the art. Also, all references cited above are incorporated herein, in their entirety, for all purposes related to this disclosure.

We claim:

1. A medical device for delivering a biologically active material to a body tissue of a patient in need of treatment, wherein the medical device comprises a plurality of struts and a plurality of non-structural elements integral with the struts, wherein the struts and the non-structural elements comprise the biologically active material.

2. The medical device of claim 1, wherein the non-structural elements project from the struts and are configured in a shape selected from the group consisting of a cone, a truncated cone, an oval, a straight rod, a bent rod, and a rod having heads at the ends.

3. The medical device of claim 1, wherein the non-structural elements are configured in a shape selected from the groups consisting of hoops, knots and bends, which are located along the stents.

4. The medical device of claim 1, which comprises a tubular portion comprising an outer surface, and wherein the non-structural elements are distributed throughout the outer surface.

5. The medical device of claim 1, which comprises a tubular portion comprising an outer surface, wherein the non-structural elements are located in a radially asymmetric distribution on the outer surface.

6. The medical device of claim 5, wherein the non-structural elements are distributed in a rectangular portion of the outer surface.

7. The medical device of claim 6, wherein the rectangular portion is parallel to longitudinal axis of the tubular portion.

8. The medical device of claim 7, wherein the rectangular portion and the tubular portion have same length.

9. The medical device of claim 8, wherein the surface area of the rectangular portion is from about 25% to about 75% of the entire surface area of the outer surface.

10. The medical device of claim 1, which comprises a tubular portion comprising an outer surface, wherein the outer surface has a middle section and end sections, and wherein the end sections comprise a greater number of the non-structural elements per unit length of the outer surface than the middle section.

11. The medical device of claim 1, wherein the biologically active material is selected from the group consisting of paclitaxel, actinomycin, sirolimus, tacrolimus, everolimus, dexamethasone, halofuginone and hydrophobic nitric oxide adducts.

12. The medical device of claim 1, the medical device is a stent.

13. A method for designing a medical device for delivering a biologically active material to a body tissue of a patient, wherein the medical device comprises a plurality of struts and a plurality of non-structural elements integral with the struts, wherein the struts and the non-structural elements comprise the biologically active material, wherein the method comprises:

(a) providing a preliminary medical device comprising a plurality struts in a geometric pattern wherein the struts comprise the biologically active material;

(b) determining a concentration-profile for the biologically active material which is released from the preliminary medical device; and

(c) modifying the geometric pattern of the struts of the preliminary medical device by incorporating a plurality of non-functional elements comprising the biologically active material that are integral with the struts to achieve more desired distribution of the biologically active material in the body tissue.

14. The method of claim 13, wherein the biologically active material has a minimum effective concentration and a maximum effective concentration for the body tissue, and wherein steps (b) and (c) are repeated until the body tissue to be treated is substantially free from a concentration of the biologically active material that is smaller than the minimum effective concentration and a concentration of the biologically active material that is greater than the maximum effective concentration over a desired time period.

15. The method of claim 13, wherein the biologically active material is selected from the group consisting of paclitaxel, actinomycin, sirolimus, tacrolimus, everolimus, dexamethasone, halofuginone and hydrophobic nitric oxide adducts.

16. The method of claim 13, wherein the medical device is a stent.

17. A medical device insertable into the body of a patient, which comprises an outer surface comprising a plurality of struts, wherein the outer surface has a middle section and end sections, and wherein the end sections have a greater available surface area per unit length of the outer surface than the middle section.

18. The medical device of claim 17, wherein at least a part of each of the middle section and the end sections of the outer surface comprise the biologically active material.

19. The medical device of claim 17, wherein struts located at the end sections have a greater surface area by having a more porous surface than struts located at the middle section.

20. The medical device of claim 19, wherein the struts located at the end sections are comprised of a porous material and the struts located at the middle section is comprised of a less porous material.

21. The medical device of claim 20, wherein the struts located at the end sections are covered with the porous material, and the struts located at the middle section are covered with the less porous material.

22. The medical device of claim 17, wherein the average diameter of the struts located at the end sections is greater than the average diameter of the struts located at the middle section.

23. A medical device insertable into the body of a patient, which comprises an outer surface comprising a plurality of struts, wherein the outer surface has a middle section and end sections, and wherein the end sections a greater affinity for the biologically active material area per unit length of the outer surface than the middle section.

24. The medical device of claim 23, wherein at least a part of each of the middle section and the end sections of the outer surface comprise the biologically active material.

25. The medical device of claim 23, wherein the struts located at the end sections comprise a first matrix material and the struts located at the middle section comprise a

second matrix material, and wherein the first matrix material has a greater affinity for the biologically active material than the second matrix material.

26. The medical device of claim 25, wherein the struts located at the end sections are covered with a coating of the first matrix material and the struts located at the middle section are covered with a coating of the second matrix material.

27. The medical device of claim 25, wherein the end sections and middle section further comprise the biologically active material.

28. The medical device of claim 23, wherein at least a part of each of the middle section and the end sections are covered with a linking material, and wherein the struts located at the end sections comprise a greater amount of the linking material per unit length of the outer surface than the struts located at the middle section.

29. The medical device of claim 28, wherein the outer surface comprises the biologically active material which is linked to the linking material.

30. The medical device of claim 19, which the medical device is a stent.

31. A medical device insertable into the body of a patient, which comprises an outer surface, wherein the outer surface has a middle section and end sections, wherein at least a part of each of the middle section and the end sections is covered with a coating layer comprising a first biologically active material, and wherein the end sections carry or contain a larger amount of first biologically active material per unit length of the outer surface than the middle section.

32. The medical device of claim 31, wherein the medical device comprises a tubular portion that comprises the outer surface.

33. The medical device of claim 31, wherein the coating covering the end sections comprises a coating layer containing a second biologically active material.

34. A medical device insertable into the body of a patient, which comprises an outer surface, wherein the outer surface has a middle section and end sections, wherein at least a part of each of the middle section and the end sections is covered with a coating comprising a first biologically active material, and the middle section comprises a barrier layer placed over the coating covering the middle section for reducing the release rate of the biologically active material.

35. The medical device of claim 34, wherein the medical device comprises a tubular portion and the outer surface is at least a part of the outer surface of the tubular portion.

36. The medical device of claim 35, wherein the medical device is a stent and the barrier layer is a sheath.

37. A medical device insertable into the body of a patient, which comprises an outer surface comprising a plurality of struts, wherein the outer surface has a rectangular portion having a greater capacity for carrying or containing a biologically active material per unit length of the outer surface than the parts of the outer surface that are outside the rectangular portion, by having a greater surface for carrying or having a greater affinity for the biologically active material than the parts of the outer surface that are outside the rectangular portion.

38. The medical device of claim 37, wherein the medical device comprises a tubular portion comprising the outer surface, and the rectangular portion is parallel to longitudinal axis of the tubular portion.

39. The medical device of claim 38, wherein the rectangular portion and the tubular portion have same length.

40. The medical device of claim 39, wherein a surface area of the rectangular portion is from about 25% to about 75% of the outer surface.

41. The medical device of claim 37, wherein at least a portion of the outer surface comprises the biologically active material.

42. The medical device of claim 37, wherein the medical device is a stent.

43. A method for delivering a biologically active material to body tissue of a patient in need of treatment which comprises inserting a medical device of claim 38 into body of the patient in such a way that the rectangular portion is in direct contact with the body tissue in need of treatment.

44. The method of claim 43, wherein the biologically active material is selected from the group consisting of paclitaxel, actinomycin, sirolimus, tacrolimus, everolimus, dexamethasone, halofuginone and hydrophobic nitric oxide adducts.

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RELATED PROCEEDINGS APPENDIX

There are no related proceedings.